UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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OPHTHALMIC DEVICES PANEL

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March 14, 2014
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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DAVID B. GLASSER, M.D.	Temporary Voting Member
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M E E T I N G

(8:05 a.m.)

DR. HIGGINBOTHAM: It is now 8:00, and I think we can begin. I'd like to call this meeting of the Ophthalmic Devices Panel of the Medical Devices Advisory Committee to order. My name is Dr. Eve Higginbotham, and I will be the Chair of this Panel today. I am a glaucoma specialist and a Professor of Ophthalmology, a Vice Dean, as well as a Senior Fellow at the Leonard Davis Institute at the University of Pennsylvania in Philadelphia.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application for the Visian Toric Implantable Collamer Lens, sponsored by STAAR Surgical Company.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation.

So I'd like to begin with Dr. Eydelman.

DR. EYDELMAN: Good morning. My name is Malvina Eydelman. I'm the Director of the Division of Ophthalmic and ENT Devices

here at the FDA. Welcome, everyone.

DR. CHAPPELL: Good morning. I'm Rick Chappell, Professor in the Department of Biostatistics and Medical Informatics at the University of Wisconsin, Madison. I'm particularly interested in clinical trials and their methodology, the analysis and design.

DR. MACSAI-KAPLAN: Good morning. I'm Marian Macsai, specialist in cornea external disease refractive surgery, Professor of Ophthalmology at University of Chicago.

DR. COLEMAN: Good morning. Anne Coleman. I'm a Professor of Ophthalmology and Epidemiology at UCLA, and I'm a glaucoma specialist.

DR. GLASSER: Good morning. I'm David Glasser. I'm in private practice in cornea and external disease in Columbia, Maryland and on the part-time faculty at Hopkins and University of Maryland.

DR. SAHEB: Good morning. I'm Hady Saheb, Assistant Professor of Ophthalmology at McGill University, Montreal, and a glaucoma specialist and cataract surgeon.

DR. HUANG: Good morning. I'm Andrew Huang. I'm Professor of Ophthalmology at Washington University in St. Louis. I'm a cornea specialist.

MS. FACEY: Natasha Facey, Designated Federal Officer, FDA.

DR. JENG: I'm Bennie Jeng, Professor and Chair, University of Maryland School of Medicine in Baltimore, cornea and external disease

specialist.

DR. WEISS: Jayne Weiss, Professor and Chair at LSU in New Orleans, cornea and refractive surgeon.

DR. CHAMBERLAIN: Win Chamberlain, Associate Professor at the Oregon Health and Science University. I'm a cornea and refractive surgeon.

DR. ZABRANSKY: Ron Zabransky. I am a retired microbiologist. I don't know why I'm here in some ways. However, I have served on medical device panels, quite a few, over the past 20 years. I'm a retired pathology professor from Case Western Reserve School of Medicine.

MS. SCHWARTZOTT: Hi, I'm Jennifer Schwartzott, and I'm the Patient Representative. I'm also the New York chair leader for the United Mitochondrial Disease Foundation, and I had a toric lens implanted in October of last year and will be having one implanted in the right eye sometime this year.

MS. LATIMER: Good morning. I'm Jody Latimer. I'm a occupational health nurse, public health nurse with Woodward, Incorporated in Colorado.

MR. PFLEGER: Good morning. Michael Pfleger. I'm the Industry Rep. I'm the head External Affairs and Regulatory Policy for Alcon, a division of Novartis.

DR. HIGGINBOTHAM: Thank you, Panel members.

Members of the audience, if you have not already done so, please sign the attendance sheets that are located on the registration table directly outside of this room.

Ms. Natasha Facey, the Designated Federal Officer for the Ophthalmic Devices Panel, will now make some introductory remarks.

MS. FACEY: Good morning. I will now read the FDA Conflict of Interest Disclosure Statement.

The Food and Drug Administration is convening today's meeting of the Ophthalmic Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have

financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employees. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application of the Visian Toric Implantable Collamer Lens, sponsored by STAAR Surgical Company. The device is intended to be placed entirely within the posterior chamber directly behind the iris and in front of the anterior capsule of the human crystalline lens.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in connection with 18 U.S.C. Section 208.

Michael Pfleger is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Alcon

Incorporated.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

For the duration of the Ophthalmic Devices Panel Meeting on March 14th, 2014, Ms. Jennifer Schwartzott has been appointed to serve as a Temporary Non-Voting Member. For the record, Ms. Schwartzott serves as a consultant and patient representative to the Cellular Tissue and Gene Therapies Advisory Committee in the Center for Biologics Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

The appointment was authorized by Jill Hartzler Warner, Acting Associate Commissioner for Special Medical Programs on March 10th, 2014.

Appointment to Temporary Voting Status.

Pursuant to authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I appoint the following individuals as voting members of the Ophthalmic Devices Panel for the duration of this meeting on March 14th, 2014:

Dr. Jayne Weiss, Dr. Winston Chamberlain, Dr. Ronald Zabransky, Dr. Andrew Huang, Dr. David Glasser, Dr. Anne Coleman, Dr. Hady Saheb, Dr. Marian Macsai-Kaplan, Dr. Richard Chappell, and Dr. Bennie Jeng.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This statement was signed by Dr. Jeffrey Shuren, Director of the Center for Devices and Radiological Health, on March 6th, 2014.

Before I return the meeting back over to Dr. Higginbotham, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated, and they can be contacted at 410-974-0947.

Information on purchasing videos of today's meeting and handouts for today's presentations are available at the registration table outside the meeting room.

The Press Contact for today's meeting is Susan Laine.

I would like to remind everyone that members of the public and press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing session and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with AnnMarie Williams at the registration table.

In order to help the transcriptionist identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Dr. Higginbotham?

DR. HIGGINBOTHAM: This is Dr. Eve Higginbotham. We will now proceed to the Sponsor's presentation. I would like the Sponsor to approach the podium.

I will remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

The Sponsor will have 100 minutes to present. You may now begin your presentation.

MR. CALDWELL: Thank you and good morning. I'm

Barry Caldwell, President and CEO of STAAR Surgical. We're honored to be here today on a nice, non-snowy day to present the PMA supplement for the Visian Toric Implantable Collamer Lens, or Toric ICL. The data from this supplement demonstrate that the Toric ICL provides a safe and effective option for patients with refractive myopia and astigmatism.

STAAR Surgical has been a publicly traded company for more than 30 years. We have nearly 350 employees focused on developing innovative intraocular lenses and delivery systems. Over the past four years, we've been doing just the opposite of many U.S. companies. We're proud to say that we're moving manufacturing jobs from outside the country into the U.S. Our Monrovia, California facility is ISO 13485 certified, and we completed the FDA BIMO inspection for this supplement in August of 2013.

The supplement you're reviewing today is for the Toric ICL, but you're also going to -- we're going to share a lot of data today on the Visian Implantable Collamer Lens, or Myopic ICL. The Myopic ICL is the parent lens of the Toric ICL. The Myopic ICL has been in the market for over 17 years worldwide. More than 300,000 Myopic ICLs have been implanted globally since 1997, and of these, more than 45,000 have been implanted here in the U.S. since 2005. You're also going to hear the number over 400,000 quoted. That's the total number of Myopic and Toric ICLs that have been implanted globally. I'm not sure, but I doubt there have been many implantable devices with over 400,000 implants that have been before the Panel.

As you'll also see today, we have a very low rate of complications. And it's at 1.26%. And also, importantly, there have been no reported cases of an explant due to non-traumatic endothelial cell loss.

Today in the U.S., the correction of myopia and astigmatism requires two procedures, one to address the myopia and a second to correct the astigmatism. This second procedure brings additional risk and can lead to additional variables. The Toric ICL eliminates the need for this second procedure. It allows for a single treatment for myopic astigmatic patients.

The Toric ICL is nearly identical to the Myopic ICL. In fact, the only difference is the addition of a toric surface on the anterior side of the optic. The surgical technique is also nearly identical. The only change is the alignment of the axis of astigmatism.

Since 2002, the Toric ICL has been commercially available outside the U.S. It has been implanted in more than 110,000 eyes in more than 60 countries where it is approved for use. Given their similarities, the only change in the indications statement from the Myopic ICL to the Toric ICL is the addition of cylinder ranges for astigmatism.

The U.S. trial for the Myopic ICL began in 1997. The first patient in that cohort has had the Myopic ICL implanted for more than 15 years. Following U.S. approval of the Myopic ICL, we initiated three post-approval studies. Two have been completed, a five-year follow-up to collect data on adverse events, including endothelial cell loss, and a study on axial

length. The third post-approval study is designed to follow the incidence of cataracts, corneal decompensation, and elevated IOP; 3,000 eyes have been enrolled in this study, and they will be followed for five years.

While the Myopic ICL trial was underway, STAAR initiated the Toric ICL trial. As you've read in the Agency's Executive Summary, our clinical and regulatory compliance was lacking on this trial. Our protocol deviations were too high, and we had poor BIMO audits in 2003 and 2007, which helped to lead to an integrity hold on this submission in 2007. We appreciate the FDA's diligence throughout this process. We wish we had more closely followed the compliance guidelines. But we did not. We clearly messed up.

But since 2007, we've worked hard to make changes. I joined STAAR as President and CEO at the end of 2007. We began to install -- well, let me tell you a little bit of my history. I've been in the ophthalmic medical device history for over 30 years. I started out with a little company called Cavitron in the original phacoemulsification technology and remained as Cavitron became CooperVision, and then later Alcon.

When I came on board at STAAR, we began to install a new senior management team. And with this team, we've initiated a number of new procedures to achieve compliance. We've introduced ongoing training and identification of key objectives. We've increased monitoring and improved communication between functional disciplines and locations. These changes are making a difference.

Over the past two years, we've had four FDA inspections, three of which resulted in no observations, and the fourth resulted in observations which appeared to not warrant regulatory follow-up at this time. This is the type of environment we're working every day to build at STAAR. And we know the process doesn't stop here. We remain committed to continuously improving our organization.

Understandably, the FDA placed this trial on an integrity hold in 2007. We then initiated an independent audit of 100% of the data across the seven clinical sites. The FDA directed the audit team, which thoroughly reviewed 92,000 data points over the course of 18 months. The audit affirmed the data's integrity, with a small percent of the data points changed. As a result, the submission was taken off integrity hold in 2009. Given the improvements we made at STAAR and the results of this audited data, we're proud to present the results of the Toric ICL study.

As you'll see today, the audited clinical outcome data clearly support the effectiveness and safety of the Toric ICL. After surgery, uncorrected visual acuity was 20/20 or better in 82% of the eyes implanted with the Toric ICL. And 54% of the eyes were 20/16 or better. Post-op, 77% of eyes had uncorrected visual acuity equal to or better than their pre-op best-corrected vision, and nearly half saw better uncorrected post-op than they saw with their glasses or contact lenses. And there were no new safety signals observed in the Toric ICL. The safety profile was consistent with that

seen with the Myopic ICL.

In addition to reviewing the efficacy and safety outcomes, here's what you'll hear from us today. There's a clear unmet need for the Toric ICL in the U.S. The Toric ICL is built upon an already approved platform, and the data demonstrate that it's a safe and effective option for myopic patients with astigmatism.

Post-approval studies and peer-reviewed literature show the ICL platform is both time-tested and adverse event rates are low. And patients are very satisfied with the Toric ICL.

So, in summary, the clinical trial data and post-approval experience demonstrate that the benefits of the Toric ICL outweigh the potential safety risk.

This morning you'll hear from Dr. Robert Rivera, who is Director of Clinical Research at Hoopes Vision; Robin Hughes, Vice President of R & D and Regulatory Affairs at STAAR Surgical. Dr. Steve Schallhorn, Founder of the Department of Defense Refractive Surgery Program; Dr. John Vukich, Assistant Clinical Professor at the University of Wisconsin; and Dr. Francis Price, Founder of the Corneal Research Foundation of America. And as you can see behind me, there is a good-looking group of folks who will help us in answering your questions today. Included in that group is Dr. Gerard Smits and Dr. Ed Sarver.

Madam Chairman, I'd like to thank the Panel for this

opportunity.

Dr. Eydelman, I want to thank the FDA and your team. And it's an honor for us to be here today to have this opportunity.

Now I'd like to introduce Dr. Robert Rivera, who will discuss the current treatment options for patients with myopia and astigmatism.

Dr. Rivera?

DR. RIVERA: Thank you, Mr. Caldwell.

And good morning, members of the Panel. What a pleasure it is to be with you this morning. I really appreciate this opportunity to discuss this particular study that was performed.

I am actually a refractive surgeon and Director of Clinical Research at Hoopes Vision in Salt Lake City. My previous practice in Arizona was involved in the registration trials for the Myopic and the Toric ICLs. And I am a paid consultant to the Sponsor and a shareholder as well. I routinely treat patients utilizing all of the vision correction options available today.

Now, today I'd like to begin by discussing the epidemiology of myopia and astigmatism, review with you the current treatment options for myopic patients with astigmatism, and then introduce some specifics of the Toric ICL and how the lens can actually benefit our patients.

Let's start with the epidemiology of astigmatism and myopia. The prevalence of myopia is variable, depending on age, gender, and race. A study reported in the National Health and Nutrition Examination Survey used

an auto refractor to obtain data on astigmatism and other refractive areas in more than 12,000 subjects, ages 12 years and older. The study found that the age-standardized prevalence of myopia was just over 33% while the prevalence of astigmatism was slightly higher, at just over 36%. But interestingly and very importantly, the estimated prevalence of myopia in people age 12 to 54 has actually increased from 25% to 41.6% since 1972.

This slide shows the distribution of astigmatism from a database of over 11,000 spectacle prescriptions. And as you can see, about 31% of myopes, shown in the yellow bars, had at least 1 diopter of astigmatism, and at every cylinder power breakdown, myopes had more astigmatism than hyperopes.

So let's consider the current treatment options for patients with astigmatism and highlight the unmet clinical need for this substantial group of patients. The three main treatment options available in the U.S. today are these: Nonsurgical are, of course, spectacles or contact lenses. But, unfortunately, these solutions may be limited by the activities that patients participate in, their ocular health, the severity of their prescription, recurring costs and accidental loss, to name a few. Surgical options include laser procedures, such as LASIK and PRK. These are very commonly performed, but there are important limitations to consider. And as we all know, these procedures involve a permanent ablation of corneal tissue to reshape the cornea, but they carry the potential for complications, such as

creating corneal irregularities, progressive thinning of corneal tissue, and dry eye.

Nonlaser options, by the way, are those which create incisions such as astigmatic keratotomy and limbal relaxing incisions. But these procedures only treat astigmatism and involve creating a deep corneal wound to alter the corneal curvature. These procedures can only be successfully performed by a skilled and experienced surgeon, but the outcomes, nonetheless, can be quite variable and unpredictable.

Now, despite the currently available treatment options, we still find a significant unmet clinical need for myopic patients with astigmatism who desire spectacle independence. For example, for patients who receive a Myopic ICL but also require astigmatic correction, we now have to perform a second procedure. And as I mentioned, these additional procedures come with their own risks and limitations. Unfortunately, there is a substantial group of patients who are not good candidates at all for laser or incisional procedures due to such factors as preexisting irregular corneas and higher refractive errors.

Now, in practice, we also encounter patients who wish to avoid laser or incisional procedures. They may have specific concerns about permanent removal of corneal tissue or prolonged visual recovery. This is particularly true for patients with high occupational risk, such as athletes and military personnel. Now, currently, these two groups of patients can only

have their myopia corrected with a Myopic ICL, but their astigmatism remains uncorrected.

So in light of these limitations, what significant benefit could the Toric ICL offer these patients? The major benefits of the Toric ICL are outlined here. First, it requires only refractive procedure and thus eliminates potential risks associated with a secondary procedure. The Toric ICL is implanted via the same minimally invasive procedure that's already in use for the Myopic ICL. The Toric ICL, like its myopic counterpart, is completely removable through the same small incision used for its implantation. If removed, this generally allows the patient to return to their preoperative best-corrected acuity. And, finally, the Toric ICL, like the Myopic ICL, preserves the preexisting corneal shape since no tissue ablation is required.

So now let's discuss some specifics of the lens design. Shown here is a diagram of the Toric ICL. The lens has three distinct sections beginning with the optic, which provides the refractive power, the haptic section provides the elevation and vault, while the flexible footplates position the lens and provide rotational stability. I need to point out that the only difference between the previously approved lens, the Myopic ICL, and the new Toric ICL is the addition of astigmatic correction on the anterior surface of the lens optic.

The Toric ICL, in fact, has its cylinder correction on a range of axes, and these axes are relative to the horizontal, or 0- to 180-degree

meridian. The diamond-shaped markings at the side of the optic are there to ensure proper orientation of the lens once inserted. The multiple axes are designed to limit the amount that the lens needs to be aligned with in the eye to correspond to the axis of the patient's correction. Given these four axes, the lens will not require any more than 22.5 degrees of alignment for correcting of the patient's astigmatism.

So now I'd like to explain how the Toric ICL is implanted. For reference, here is an image of the eye without the ICL, and here, shown in blue, is the ICL in its position. The flexible footplates are designed to bend and mold to the shape of the ciliary processes, which ensures rotational stability. The haptics vault the Toric ICL over the patient's crystalline lens, and the iris now rests on the anterior surface of the implant. This creates an interaction between the iris and the lens which helps to hold the lens in position.

One important thing to remember is that the sulcus is actually -- has a radial pattern of ridges and valleys which are formed by the ciliary processes and the pars plicata, as illustrated here. The footplates of the Toric ICL are such that they find a fixation point among these ridges, which establishes rotational stability.

Now, if you'll look here, this is an animated schematic of how a lens with cylinder correction at 35 degrees is used to correct the patient's 55-degree axis of astigmatism. In this example, the lens is simply aligned 20

degrees counterclockwise from the horizontal meridian, which brings the toric axis of the lens into alignment with the patient's axis of astigmatism at 55 degrees. This is what is known as the fixation angle, in this case, 20 degrees.

The only difference between the Toric ICL and the Myopic ICL being the correction on the anterior surface for astigmatism, the Toric ICL is implanted using the exact same surgical technique as its Myopic counterpart. The Toric ICL is implanted within the posterior chamber, directly behind the iris and in front of the anterior capsule of the human crystalline lens through a 3.5 mm or smaller incision. And once implanted in the posterior chamber, the Toric ICL is positioned, then, according to the surgical plan for axis placement. Now, as I mentioned here, the lens is designed so that it requires no more than 22½ degrees of alignment after implantation.

The Toric ICL footplates are designed to reside within the ciliary processes and are actually quite forgiving with respect to sizing. The label recommends white-to-white measurement for sizing, but it also recognizes that newer technology is available. In fact, since this study was concluded, a number of refinements in ultrasound biomicroscopy, or UBM, may now allow a direct measurement of the sulcus diameter for Toric ICL sizing.

This table shows a similarity, in fact, between the proposed Toric ICL and currently available Myopic ICL models. As you can see, the spherical equivalent power and overall length are the same between the two

lenses, but the only difference between the Toric and the Myopic models is the toric power itself.

So, in conclusion, we've noted that there is a broad range of patients who would benefit from the Toric ICL. These include patients eligible for the Myopic ICL who also require astigmatic correction, patients with astigmatism who are not good candidates for a laser or incisional procedure, and those who prefer a non-laser or incisional approach. Of utmost importance to these patients and their surgeons, the Toric ICL can correct both myopia and astigmatism in one single step and thereby eliminate the risks of secondary procedures. Just as with the Myopic ICL, the Toric ICL does not reversibly alter the cornea with the added benefit of being removable.

Thank you for your time. Now I'd like to introduce Robin Hughes, who will present the study methods and discuss the conduct of the Toric ICL study.

Mr. Hughes?

MR. HUGHES: Thank you, Dr. Rivera. My name is Robin Hughes. I'm Vice President of Research and Development and Regulatory Affairs at STAAR.

In my presentation, I will review some of the methods used in the Toric ICL clinical study along with some of the elements of study conduct and the independent audit of the clinical database.

In study methods, I will explain the impact of having the lenses

packaged in saline during the study and why we changed the packaging to a balanced salt solution for commercial use. I will also review the methods used to determine lens power and lens length.

Before talking about the Toric ICL study, let me start with our experience with the approved Myopic ICL. All lenses in the Myopic ICL study were packaged in saline. When a lens packaged in saline is implanted into the eye, the size and power of the lens changes. This is due to differences in the composition of saline compared to the fluid in the eye, the aqueous humor. There are simple conversion factors used to calculate the changes. The lens increases in size by 5% and in doing so absorbs water, which lowers the refractive index and decreases the power by 22%.

During the Myopic ICL study, the calculation software used for lens selection took this difference into consideration. It calculated the lens power and size needed in the eye, converted them into the power and size in saline, and then recommended the appropriate lens.

During the review of the Myopic ICL study, the FDA expressed concerns that lenses packaged in saline were not labeled to reflect the power of the lens in eye and that this needed to be addressed before the product was commercialized. Based on this input, STAAR changed the packaging solution to BSS. Since BSS is equivalent to the aqueous humor, the lens size and power packaged in BSS are the same as in the eye.

When this change was made, it was submitted and accepted by

the Agency, and since our U.S. launch in 2005, more than 45,000 Myopic ICLs have been implanted in the U.S., all of which were packaged in balanced salt solution.

Now to the lenses implanted in the Toric ICL study. Again, all of these lenses were packaged in saline. And just as we did with the Myopic ICL, we plan to commercialize the Toric ICL in BSS. To make the data easier to review, after discussions with the FDA, we converted all lens powers and lengths in the submission to reflect lenses as packaged in BSS. These are the ranges that you'll see in our results today.

To illustrate what this means, let me look at the ranges of lens powers and sizes studied versus those which STAAR is seeking approval. The first column under "protocol" shows the range of lens sizes and powers spherically equivalent in cylinder as per the protocol for saline and BSS. The key numbers to focus on are the lengths and powers in BSS since these reflect the power and the length of the lens in eye.

Moving to the next two columns under "studied and approved MICL," these columns show the lengths and power either implanted in the study or as approved for the Myopic ICL. And as you can see, our proposed ICL parameters were either evaluated in the Toric ICL study or approved for the Myopic ICL.

Now to the method for determining lens power. This was done using the Toric ICL calculator software. The user entered the values shown

here. This software did not compensate for surgically induced astigmatism. At the time of the study, the impact of surgically induced astigmatism, or SIA, was not as well understood as it is today.

So let's look more closely at the impact of surgically induced astigmatism. During the toric study, keratometry data was collected preoperatively and postoperatively at the 3- and 12-month visits. Using this data, the spatial median SIA was determined to be 0.22 diopters at 83 degrees; this created by the temporal incision. This level of SIA was supported by the outcome data, such as the reduction in absolute cylinder across the overall power range.

So while the results were very good without compensating for surgically induced astigmatism, we realized such compensation has the potential to further improve outcomes, and we're currently investigating and intend to include compensation for SIA in a future version of the calculated software.

The calculated software determined the effective lens power required at the ICL plane to achieve emmetropia within the eye. Then using this calculated power, the software displayed a range of power showing the expected outcomes for each of the lenses in that range. It showed the expected sphere, cylinder, axis, and spherical equivalent. In general, the user would select the lens with an expected SEQ closest to 0 without overcorrecting the myopia or the astigmatism.

As Dr. Rivera mentioned, since the Toric ICL can be positioned by up to 22½ degrees to align lens cylinder to axis of astigmatism, the calculator then displayed a range of lenses with the correct power within 22 degrees of the desired axis. The user then selected a suitable lens, and the software generated an implantation orientation diagram that provided the surgeon with guidance on lens alignment in the eye.

And here we see a sample of the implementation orientation diagram. In this example, the axis of astigmatism was 75 degrees, and the lens cylinder selected was 86 degrees. In order to align the two axes, the lens would need to be aligned by 11 degrees clockwise. So, in this example, the lens will be positioned with a fixation angle of 11 degrees. Postoperative lens position and observed rotational stability will be assessed relative to this lens position.

Moving on to the method used for determining length. In the study, we used white-to-white measurement combined with anterior chamber depth. And here is an excerpt from the lens length lookup table. In this example, the recommended lens length for an eye with a white-to-white measurement of 11.8 mm would either be 12.6 or 13.2 mm depending on the anterior chamber depth.

So now turning to study conduct. In the effectiveness presentation, Dr. Schallhorn will review the overall protocol deviations and provide a clinical perspective. But first I'd like to review the technical aspects

of a group of protocol deviations being referred to in the FDA Executive Summary as lenses not according to protocol. Within this group, there are three categories: sphere and cylinder outside the approved range, axis outside the protocol-specified four axes, and lens length not selected by the approved method. In some instances, there was overlap between the three categories, giving us a total of 143 eyes in which this protocol deviation was observed.

There were 32 eyes in which the labeled power of the lens implanted was outside the range approved in the protocol. But it's important to point out there were no patients with preoperative refractions that were outside the protocol-approved treatment range. The majority of the eyes in which the lens was outside the approved range had cylinder power less than 1.5 diopters. The reason these were outside the protocol-approved range was due to a simple error in the protocol that stated that a 1.5-diopter cylinder lens was required to correct 1 diopter of manifest cylinder. The protocol should have stated that a 1 diopter cylinder lens was needed to correct 1 diopter of manifest astigmatism.

The reason we saw cases of axis outside the protocol-specified four axes was because of a change in our manufacturing procedures. When we designed the study, we planned to manufacture the lenses based on four axes: 0, 45, 90, and 135. This is what was specified in the protocol. However, shortly after initiation of the study, we began commercial use in other

markets. And when surgeons were ordering a lens not in inventory, they expected the lens with an axis target closer to their patient's actual axis. So we changed our manufacturing process to increase the number of available targets from 4 to 33. Unfortunately, some of these lenses we used in the study and we failed to communicate the change to FDA.

So the 126 lenses implanted with these new axis targets are considered protocol deviations. However, STAAR does not believe this change had any impact on the outcome of the study, and here's why. If there were any impact from this change, it would have affected the range of fixation angles used in the study. Remember, the fixation angle is the angle at which the lens is positioned in the eye to align the cylinder with the cylinder of astigmatism. One might expect lenses manufactured with 33 axes at approximately 5-degree intervals would require less -- a lesser angle of alignment in the eye. However, since the vast majority of lenses were selected from inventory rather than being made for a specific patient, this was not the case.

And when we conducted a comparison between lenses manufactured on the 4 axes versus the 33, it showed there was no statistical difference in terms of the average fixation angle. The p-value was 0.67. It also showed there was no statistical significant difference in the distribution of angles between the two groups.

Now to lens length. There were 18 lenses implanted with lens

difference from the recommended length. Of these, 11 were requested by the investigator, primarily based on the surgeon's experience with the patient's primary eye. These resulted in lenses being implanted that were both longer or shorter than recommended. Four were 14.3 mm lenses, a lens not included in the protocol and for which we are not seeking approval. And three was sized using an incorrect ACD measurement that incorporated the corneal thickness into the measurement and resulted in the implantation of longer lenses. But, again, STAAR does not believe these deviations affect the outcomes. And Dr. Schallhorn will address the overall statistical significance of these deviations along with the previous two categories in his effectiveness presentation.

Finally, I'd like to turn your attention to the independent audit of the Toric ICL study database. As Mr. Caldwell mentioned, in 2007, we initiated an independent audit of our entire clinical database for the Toric ICL under the direction of FDA. This audit covered over 92,000 data points and took 18 months to complete. ProMedica was the independent auditor, and they reported directly to FDA.

They audited 100 percent of the clinical data at all seven sites, from the patient charts to the case report forms, and then from the case report forms to the database. Based on this audit, 238 data points were changed. This represented 0.3% of the total data points in the study. However, 158 were typographical or transcription errors, leaving only 80 data

changes that were considered by the auditors to be clinically relevant. And, in fact, the changes actually improved the results by a 10th of a percent in some areas but overall had no significant impact on the study outcomes.

After reviewing the data, ProMedica concluded the corrected database is a true reflection of the data in the field, and the corrected database can be used to analyze this data. Based on these findings, as Mr. Caldwell mentioned, the integrity hold was lifted from the submission in 2009.

So, in conclusion, the range of lens powers and lengths for which we are seeking approval is consistent with those studied. All lenses implanted in the study were for refractions that were within the treatment range approved in the protocol. And other than changes to axis targets, these lenses were the same design that we used throughout the study.

I'd now like to invite Dr. Steve Schallhorn to share the effectiveness data from the Toric ICL study. Thank you.

Dr. Schallhorn?

DR. SCHALLHORN: Thank you, Mr. Hughes.

My name is Steve Schallhorn. I'm an ophthalmologist in San Diego. I spearheaded the Military Refractive Surgery Program until my retirement, and now I'm in private practice. I'm also a Professor of Ophthalmology at the University of California San Francisco and the Chief Medical Director for Optical Express. I'm a paid consultant to the Sponsor,

and I will be presenting the effectiveness data from the Toric ICL study.

What I'd like to do for the next few minutes is describe the study design and study conduct, including details of all protocol deviations. I will then present information about the study population followed by the effectiveness results.

First, the study design. The design for this study was based on FDA guidance in place in 2001, and the protocol was approved by the FDA in 2002. This is a prospective study with seven surgical sites. Patient enrollment was initiated in August 2002 and was completed in January 2006. Since the previously approved Myopic ICL established the safety of the ICL platform, the primary objective of the Toric ICL study was to assess the effectiveness of the lens for correcting moderate to high myopic astigmatism. The primary effectiveness endpoint analysis was at the 12-month visit.

Inclusion criteria were reflective of patients who would be treated in clinical practice. Age between 25 to 45 years old -- 21 to 45 years old with vision correctable to 20/40 or better. Eligible subjects had to be phakic with moderate to high myopia and refractive astigmatism of +1 to +4 diopters. Patients with conditions that could preclude good visual outcomes were excluded from the study. Patients with diabetes, glaucoma, and significant lens capacities were also excluded as were eyes that had previously undergone intraocular or refractive surgery.

The effectiveness endpoint for the Toric ICL included an

improvement in uncorrected visual acuity, a decrease in myopia and cylinder, refractive predictability, stability of sphere and cylinder, patient-reported outcomes, and the rotational stability of the lens.

Moving on to safety endpoints, as previously mentioned, the overall safety profile of the platform was established with the approved Myopic ICL. So this study was designed to show that the addition of cylinder correction would not adversely affect safety. So the safety endpoints were preservation of best-corrected visual acuity, assessment of lens opacities, intraocular pressure, and the incidence of complications and adverse events.

Now I'll spend a few minutes discussing some important aspects of study conduct, in particular, accountability and protocol deviations. As you are well aware, this study was not ideal. There were a number of protocol deviations. And we take this very seriously. It's important to understand that the vast majority of these deviations were not recognized until well after the conclusion of the trial after multiple internal reviews and submissions to the FDA. Once they came to light, STAAR thoroughly investigated each to determine the impact they may have had on the outcome of the trial.

I'd like to now share with you details about the nature of these deviations and the additional analysis that STAAR conducted. To start, I'll show you a flow diagram of the patient disposition. A total of 250 eyes were enrolled. Of these, 231 were implanted with the Toric ICL. Among these 231

eyes, 21 were excluded from the analysis, 16 fellow eyes didn't meet the inclusion criteria for astigmatism so they were implanted with a Myopic ICL per protocol, 2 were out of age limit at the time of surgery, and 1 eye had astigmatism of less than 1 diopter. There were also two compassionate waivers approved by the FDA.

This resulted in an analysis of 210 eyes, including 124 primary and 86 fellow; 13 eyes were lost to follow up, and 3 were discontinued. So, ultimately, 194 eyes were evaluated at the 12-month visit. Of these, 48 eyes were seen out-of-window at the 12-month visit, generally a few months later. I will discuss these in more detail in a few moments.

But, first, I'd like to review the key protocol deviations and their clinical relevance. Protocol deviations affected 4% of the data points in the study. All deviations have been characterized as major or minor, according to standard convention. Specifically, a major protocol deviation included any deviation that could potentially affect the subject's safety, well-being, or integrity of the data, and a minor deviation included any other departure from the protocol.

First, let me go through the major deviations. As Mr. Hughes discussed, there were 32 lenses where the sphere or cylinder was outside of the approved range, but remember, the error was in the writing of the protocol. These lenses were included in the effectiveness analysis because they were the correct power to treat the patient. We also included the 18

lenses where the lens length was not selected per protocol because the lens length has no effect on optical power.

Now let's discuss the minor protocol deviations. Missing information accounted for the highest number of deviation occurrences. The majority of these were items from the subjective questionnaire, for a total of 220 missed data points, 216 of which were from 24 visits where the entire questionnaire was unfortunately not completed by the patient. There were also 23 visits where the postop lens orientation position was not recorded. Multiple imputation and last observation carried forward imputation were performed for refractive and visual outcomes. Every -- even imputation of worst-case values showed that these missing data points did not affect the outcomes.

Mr. Hughes covered this deviation, so let me summarize. There were a number of lenses that were outside of the protocol-specified manufacturing axis target. But other than an increase in the number of axis targets, all of these lenses were of the same design. This protocol deviation did not result in any clinical or surgical issues. All of the lenses were properly aligned to correct the astigmatism and did not require more than 22 degrees of rotation after implantation.

At the 12-month exam, there were 48 out-of-window visits, 12 early and 36 late. More than half of the out-of-window visits occurred at the Navy site as a result of patients being unexpectedly deployed overseas. So

what impact did these have? The 36 late visits should not affect outcomes. In fact, the Toric ICL is a permanent device. So late visits provide useful long-term safety and stability data. Of the 12 eyes that were seen early, 8 were fellow eyes that were examined during the in-window visit of the primary eye. As I will show you in a minute, STAAR has done a careful analysis of these out-of-window visits, which demonstrates they had no impact on the study outcomes. Based on the extensive review, it is appropriate to include these out-of-window visits in the effectiveness analysis.

There was also deviation for 41 eyes that were included in an unapproved randomized sub-study at the Navy site. Subjects at this site were randomized to either the Toric ICL or PRK. Those randomized to the Toric ICL followed the approved protocol and were included in the analysis cohort. In addition, there were 33 missed visits, and 33 identified occurrences where Snellen charts were used instead of ETDRS. The use of Snellen charts likely occurred because some of the study sites were also involved in the concurrent Myopic ICL study that used the Snellen charts, so there was some confusion about which chart to use.

75% of protocol deviations were simply because the case report forms did not have a place for the information required in the protocol. For example, there was missing case report data on pre- and post-operative medications. While it was not on the case report forms, this data would have been recorded in the medical records. We do not believe these

issues impact the safety or effectiveness endpoints of the study.

There were also eight occurrences of noncompliance with presurgical procedures. In six cases, the iridotomy was done prior to the two-week visit, and two did not have a stable refraction for the 12 months prior to study entry. And, finally, three eyes were outside the inclusion criteria.

Now that we've discussed the deviations, you can understand why we concluded that they would not have any impact on the study outcomes. But to further evaluate this, the Sponsor conducted multiple sensitivity analysis on out-of-window visits, major protocol deviations, and lenses implanted not according to protocol to see if these deviations had any impact on outcomes. Five key target endpoints were evaluated: manifest refractive spherical equivalent, or MRSE, cylinder outcomes, uncorrected and change in best-corrected vision. Please note that these five analyses I'm going to show you have not been submitted or reviewed yet by the FDA.

First, here is a sensitivity analysis for MRSE. It clearly demonstrates that the presence or absence of out-of-window visits, major protocol deviations, or the lens outside approved protocol did not significantly change the mean spherical equivalent outcome.

We see if the same holds true for cylinder outcome. We concluded that the presences or absence of out-of-window visits, major protocol deviations, or the lens outside protocol did not significantly change the mean cylinder outcome.

Here's a sensitivity analysis for percent change in manifest cylinder. Again, there were no significant differences for any of the criteria. The analysis for the likelihood of achieving at least 20/20 uncorrected vision also shows that none of the variables caused a significant change.

And, finally, when we look at preop to postop change in best-corrected vision, as in all previous analyses, the presence or absence of out-of-window visits, major protocol deviations, or the lens outside protocol did not significantly influence the change in mean best-corrected vision.

So given the nature of the protocol deviations, the remote likelihood that they would affect outcomes and the sensitivity analysis showing no outcome effect, we believe it was reasonable and appropriate to include them in order to provide a complete and accurate efficacy analysis.

Now I'd like to review the demographics and baseline characteristics of the study population. The patients who were treated represent those that seek refractive surgery. However, these patients generally had higher levels of myopia. There was a good distribution of males and females, a typical mix of ethnicity, as well as left and right eyes. The mean preoperative spherical equivalent was more than -9 diopters with up to -19.5. And the mean preoperative cylinder was 2 diopters, with a range of 1 to 4.

The study enrolled patients with a broad range of myopia, as shown here, in a distribution of preoperative manifest spherical equivalent.

Similarly, patients had a broad range of astigmatism, shown here in the distribution of preoperative cylinder.

Now let's discuss the refractive outcomes. This slide shows the mean spherical equivalent over time as well as the standard deviation. It shows there is a high degree of myopia before surgery that was effectively corrected. Two additional things to pay attention to. One is how stable the refraction was over time, and two, that there was little variance in the refractive outcomes, as indicated by the very small postop standard deviation.

We also see similar effectiveness across the range of treatments. This scatter plot shows the attempted spherical equivalent correction along the x-axis and the achieved correction on the y-axis. Every eye in the 12-month dataset is shown. Notice the tight distribution, consistent with the small standard deviation of the postop refraction, and that higher levels of myopia are corrected with similar accuracy as lower. This is not something we typically see with laser vision correction, where outcomes for higher levels of myopia tend to be much less predictable.

Looking closely at predictability, over 75% of eyes were within a half diopter of emmetropia at 12 months, significantly exceeding the protocol target of 50%. And over 97% were within 1 diopter, again, greatly exceeding the target of 75%.

And looking further at the consistency results, here, we see a

spherical equivalent before and after surgery stratified by three preoperative refractive bins. It shows that patients with higher levels of myopia experience similar refractive results as those with lower levels. And the refractive results we see postop remain stable over time.

This analysis shows that the spherical equivalent was stable early on and confirmed at 6 and 12 months. Over 90% of eyes had a change of 0.5 diopters or less over these time intervals, with an insignificant mean change. The annual equivalent mean change between 6 and 12 months was only 0.16 diopters.

The refractive outcomes observed in this trial were not surprising. They confirmed the excellent results we've seen previously with the Myopic ICL. But with the Toric ICL, we were particularly interested in evaluating cylinder outcomes. This slide shows the mean manifest cylinder over time as well as the standard deviation. The average cylinder before surgery, approximately 2 diopters, was reduced to about a ½ diopter. And as in the similar spherical equivalent result, you can see how stable the cylinder was over time. We'll talk more about that in a bit.

And similar to the spherical equivalent results, the reduction in cylinder was highly predictable. Shown here is a stratified preop and 12-month postop cylinder. The postop astigmatism was 0.5 diopters or less in nearly two-thirds of eyes, exceeding the protocol target of 40%. Similarly, over 91% of eyes had less than or equal to 1 diopter of postop cylinder, which

also greatly exceeded the target.

As you can see here, the reduction in astigmatism is high across the full range of lens powers. Shown here is the percent reduction in absolute cylinder stratified by the Toric ICL power in BSS. That is proposed for the labeling of the lens. Even for the low cylinder power, the Toric ICL effectively reduced astigmatism. The overall mean reduction was 76.7%, with a 95% confidence interval of 72.2 to 81.2%.

Finally, just as we saw with the spherical equivalent, the cylinder was stable over time. The mean yearly change in absolute cylinder was essentially zero for every interval.

Next we looked at visual outcomes. This slide shows a percent of all eyes that achieved 20/20 and 20/40 unaided vision throughout the follow-up time period. Well, most eyes could barely see the big E on the eye chart without correction before surgery. A large percentage achieved 20/20 vision, and almost all achieved 20/40 vision from one week on. And they maintained that high level of vision throughout the study.

This is the cumulative uncorrected vision at 12 months for all eyes compared with their preop best-corrected vision. Remarkably, more eyes had uncorrected visual acuity of 20/12 and 20/16 than had that level of vision corrected before surgery. And even better, in those eyes that were 20/20 or better best corrected preop, more than 89% achieved 20/20 or better uncorrected vision after surgery, and all of these eyes were 20/40 or

better. This greatly exceeds the target that 85% of eyes that were 20/20 or better best corrected preop should have 20/40 or better uncorrected after surgery.

Here we are showing the paired difference between the 12-month uncorrected vision and the preop best-corrected vision as assessed by lines on an eye chart. You can see the shift to the right indicating the higher levels -- the high level of uncorrected vision relative to preop best corrected. In fact, 77% of eyes had a postop uncorrected vision as good or better than their preop best-corrected vision.

Now we'll turn to patient satisfaction and patient-reported quality of vision. We assessed patient satisfaction and found that no patient who completed the survey was unsatisfied. In fact, almost every patient reported being very or extremely satisfied with the outcome of their surgery, and importantly, this high level of satisfaction did not diminish over time. Patients were just as satisfied at 12 months as they were at 3. Similarly, nearly every patient who completed the survey said they'd be willing to have the surgery again, a good indication of satisfaction. Finally, patients rated their quality of vision higher after surgery than before.

Finally, we looked at rotational stability. Before we get into how the rotational stability was measured, an important point to keep in mind are the outcomes we've just reviewed. If the toric lens was not rotationally stable, you would expect the refraction to change, the

uncorrected vision to worsen, and patient satisfaction to decrease. For instance, if a lens with 2 diopters of cylinder rotated 10 degrees, there should be a 0.6 diopter change in cylinder. We don't see those types of changes in the trial. Even a careful vector analysis of the change in error of angle is consistent with a rotationally stable lens. In other words, all of the outcomes remain stable over time, which is an excellent indication that the lens remains stable.

With this in mind, now let's take a closer look at the direct measurement of rotational stability. This was assessed at the slit lamp, which was the method specified in the protocol and was typically used in clinical practice at the time the study was conducted. The surgeon noted the lens position on the slit lamp by assessing the fixation marks on the lens relative to the horizontal meridian. This rotational position was then transcribed onto the case report forms using a clock-hour notation. Surgeons often noted the position more precisely than the 15-degree intervals would suggest by writing the position into the free text field on the case report form.

Using this method, lenses were rotationally stable throughout the time period. This is a paired analysis for each time period, and as observed through the slit lamp at different time intervals, almost every eye had less than 5 degrees of rotation, which greatly exceeds the current ANSI standard of 90%.

So let me summarize the effectiveness results from the Toric ICL study. Regarding postop uncorrected vision, over 80% were 20/20 or better, and remarkably the majority of eyes were 20/16 or better. In particular, when we look at the comparison of eyes with uncorrected visual acuity of 20/20 or better in the Toric ICL study compared with the Myopic ICL study, you can see the benefit that the toric correction in eyes with up to 2 diopters of astigmatism who were eligible for the Myopic ICL study.

If we look at those patients who were 20/20 or better best corrected before surgery, nearly 90% were 20/20 or better uncorrected, and all were 20/40 or better after surgery, which greatly exceeded the target. The Toric ICL was very effective in reducing both sphere and cylinder, with a high level of predictability. And no patient was unsatisfied with the surgery. These results are all the more compelling given that these patients had high levels of myopia and astigmatism before surgery.

In conclusion, the study met all effectiveness targets for the correction of myopic astigmatism across the full range of cylinder powers tested. Refractive stability was excellent. The lens was rotationally stable. Uncorrected visual acuity was excellent especially considering the level of preop myopia and astigmatism. Finally, patients were very satisfied, and nearly all rated their postop quality of vision as excellent or very good.

There were a significant number of protocol deviations. And we appreciate that the study should have been conducted more carefully.

But a comprehensive assessment showed that these deviations did not affect the outcomes. Clearly, the results demonstrate that the Toric ICL is an effective option for patients with myopia and astigmatism.

Thank you. Dr. Vukich will now review the safety data.

John?

DR. VUKICH: Thank you, Dr. Schallhorn.

My name is John Vukich. I was a principal investigator for both the Myopic ICL study and for the Toric ICL study. For the past 12 years, I have served as the medical monitor for STAAR Surgical. I'm a paid consultant to the company as well as a stockholder.

The safety profile of the Toric ICL is supported by a number of data sources. As explained earlier, the Toric ICL is a modification of the myopia correcting ICL or Myopic ICL. The safety of the parent lens was originally established in the Myopic ICL study. This study of 526 eyes included a post-approval safety study with five years of follow-up in over 300 eyes.

The Toric ICL study was designed as an extension of the Myopic ICL study to evaluate the effectiveness of the toric lens. Of course, safety data was also collected and will be compared to the Myopic ICL as well.

Additionally, we have postmarketing experience in nearly 300,000 eyes worldwide in a significant body of peer-reviewed literature to help better understand the safety profile of the ICL platform.

To clarify the source of the data that I'll be presenting, I want to call your attention to the color of the title banner. Data from the Myopic ICL study is designated by a brown title background. Toric ICL studies are shown in the blue background.

The Myopic ICL study was a three-year study that was presented to the FDA in 2003, and it formed the basis of the approval for the Myopic ICL. A follow-up of at least five years was included as a post-approval commitment. We looked at the standard safety assessments shown here, and a substudy of endothelial cell loss was also conducted.

As I mentioned, the Toric ICL was designed and powered to evaluate effectiveness. During the course of the study, we also looked at the following safety assessments. As you will see today, the safety profile of the Toric ICL in 210 eyes is consistent with that of the approved parent Myopic ICL.

Today I'll focus our discussion on the topics shown here. Endothelial cell counts were not part of the Toric ICL protocol. Dr. Frank Price will be presenting data on this topic from the Myopic ICL study following my presentation.

Okay. So let's start by reviewing the data on the preservation of best spectacle-corrected visual acuity from the Myopic ICL and Toric ICL studies. Presented here is data from the Myopic ICL study. 85% of patients achieved best spectacle-corrected visual acuity of 20/20 or better at three

years. And 98% achieved 20/40 or better. Notably, these results were maintained at the 5+ year follow-up in 331 eyes. This study population was unique from populations evaluated for other refractive surgery technologies in that only 68% of eyes could be corrected to 20/20 or better preoperatively. We believe this reflects and underscores the visual challenges these patients face associated with high levels of near-sightedness.

Here are the best spectacle-corrected visual acuity results from the Toric ICL study. As you can see, they were very consistent with those from the Myopic ICL, with 99% achieving 20/40 or better best-corrected vision at 12 months. I'd like to point out that only 82% of patients were able to achieve 20/20 best-corrected vision preoperatively. However, following Toric ICL implantation, nearly 97% were 20/20 at 12 months.

Even more dramatic improvement was seen at the 20/16 level, where 77% of patients had 20/16 or better best-corrected vision postoperatively compared to only 41% who could achieve that level before surgery.

In the Myopic ICL study, when we stratified postoperative best spectacle-corrected visual acuity by baseline manifest refractive spherical equivalent, or MRSE for short, we see that all patients at every level of myopia had preservation of 20/40 best-corrected vision with the exception of three eyes, all of which were greater than -10 diopters and none of which were able to be corrected to 20/20 or better preoperatively. I should point

out that this slide represents data from a consistent cohort of 222 eyes that were seen at five years.

Again, the results from the Toric ICL study were consistent with those from the parent Myopic ICL study. Preservation of best spectacle-corrected visual acuity follows a similar pattern, with preservation of visual acuity across the full range of myopia and 100% of patients with higher myopia achieved, 20/40 or better.

And in the Toric ICL study, when we stratified by best spectacle-corrected visual acuity of 20/40 or better by level of preoperative astigmatism, again, we observed similar results. Visual acuity was preserved across the full range of astigmatism.

Another important safety metric is lines lost versus lines gained. Presented here is five-year data from the Myopic ICL study. When we look at the change in lines of best spectacle-corrected visual acuity, 45% of eyes gained one or more lines of best-corrected acuity at five years. This contrasts with only 10% of eyes that lost one or more lines of best-corrected acuity over that same timeframe.

In the Toric ICL study, we observe a similar, in fact, better pattern, with 77% of eyes gaining one or more lines of best spectacle-corrected acuity versus only 6% with one or more lines lost. Of course, loss of lines is an important issue, and I'd like to present further details on the three patients that lost two or more lines of acuity.

One had a preoperative best spectacle-corrected visual acuity of 20/12.5. At all subsequent visits, they were 20/16 uncorrected, with the exception of the final visit, at which point they measured 20/20. Technically, this patient lost two lines of acuity from baseline but reported being extremely satisfied and would have the surgery again if offered.

The second patient had 20/40 preoperative best-corrected acuity and was 20/60 at the 12-month visit. There was no pathology noted. The clinical investigator believes that this was a case of unrecognized amblyopia, with variable best acuity in this eye.

And, finally, the third patient developed an anterior subcapsular cataract. At 12 months, their visual acuity was best corrected to 20/50, representing a three-line loss.

Now let's turn to complications and adverse events. First, I'll show you the intraocular pressure data from the Myopic ICL study. In five or more years of follow-up, there was total of 12 eyes of 8 patients that had either glaucoma or increased intraocular pressure from baseline at their last visit. Seven eyes in four patients were diagnosed with glaucoma. In all three bilateral cases, both eyes were diagnosed on the same visit. Three of the seven eyes had increased IOP at the last visit. There were an additional five eyes in four patients with increased intraocular pressure at the last visit, for a total of eight eyes with increased intraocular pressure from preop.

In the Toric ICL study, one patient had an acute intraocular

pressure rise. The patient was treated with laser peripheral iridotomy and maintained a normal intraocular pressure at all subsequent visits. There was one case of a later intraocular pressure rise, which was defined as greater than 10 mm/Hg from baseline or greater than 25 mm/Hg. This patient had a preoperative intraocular pressure of 11 mm/Hg and a pressure of 22 at 12 months. It's important to note that no patient in the study required medication for control of intraocular pressure beyond the one-month visit.

I'd now like to discuss the crystalline lens evaluation from the Myopic ICL and Toric ICL studies as well as from peer-reviewed literature. In the Myopic ICL and Toric ICL studies, crystalline lens evaluation was carried out by the investigator using a slit lamp evaluation and the standard LOCS III lens classification system. The LOCS III Scale ranges from 0 to 5.9, and under this system, 1 equates to a trace opacity. Here you can see the photographic standard that was used for grade 1. I'd like you to keep this photograph in mind since the majority of lens opacities we're going to describe were no greater than this clinical standard.

In both the Myopic ICL and Toric ICL studies, the majority of opacities were trace, similar in appearance to what you saw in the previous slide. The five-year data from the Myopic ICL study shows an increase in trace opacities. However, even with longer follow-up, only about 1% of these eyes experienced a clinically significant opacity, which is defined as a loss of two lines or greater of acuity or increase in subjective glare.

Here, we see two Kaplan-Meier estimates from the Myopic ICL study. On the left is time to clinically significant opacities, and on the right is time to any observed anterior subcapsular opacity, including those that are trace or asymptomatic. The cumulative probability estimate for the development of clinically significant cataracts over the 7+ years of follow-up was 2% whereas the percentage actually observed was 1.3. The cumulative probability estimate for the development of symptomatic and asymptomatic anterior subcapsular opacities over the seven years of follow-up was 7% whereas the percentage actually observed was 5.9.

Within the Toric ICL study, there were four eyes that had trace or mild anterior subcapsular opacities. All of these were asymptomatic. All had 20/16 or better best spectacle-corrected vision. All had 20/25 or better uncorrected visual acuity. All had an absent or mild glare score.

There were two eyes in the Toric ICL study that developed clinically significant cataracts. One of these was graded as 2+ anterior subcapsular cataract. This was the patient that was presented earlier who had three lines of loss and 20/50 best spectacle-corrected acuity at the 12-month visit. One patient had no loss of best spectacle-corrected acuity but did report increased glare. This patient underwent cataract surgery at 22 months, which resulted in 20/16 best spectacle-corrected vision. Although this finding was beyond the 12-month window for the trial, we've included it here for completeness.

Beyond what we've learned in our clinical trials, there is a large body of clinical experience with the ICL platform. As noted earlier, the ICL has been in commercial use around the world for over 17 years, and multiple peer-reviewed papers have been published on its use. The Agency has identified 43 publications that it deemed suitable for data extraction. In a review of these articles, using a weighted average, the incidence of anterior subcapsular cataracts was 3.6%. It's worth pointing out that this includes reported opacities that were asymptomatic.

Turning back to data from the Toric ICL study, surgical or perisurgical complications were defined as those that occurred at the time of surgery or in the immediate postoperative period. The Toric ICL was removed and reinserted in seven eyes. There was no loss of best-corrected acuity in any of these eyes. Three eyes underwent an additional iridotomy. One eye was observed to have a higher than anticipated forward vault of the ICL on Day 1, which resolved spontaneously and was attributed to retained viscoelastic material. At one-year postop, this patient's uncorrected acuity was 20/12.5, intraocular pressure was 11 mm/Hg, and the patient reported being extremely satisfied.

In one patient, the surgeon inserted the ICL upside down. This was recognized and removed immediately, but during removal, the implant was damaged, and a new eye cell was implanted two weeks later. At one year postop, this patient's uncorrected visual acuity was 20/20, and best

spectacle-corrected visual acuity was 20/16. There was no crystalline lens opacity noted, no increase in glare score, and the patient reported being extremely satisfied.

I'd now like to discuss secondary surgical interventions seen in the clinical trials as well as in our postmarketing surveillance. In addition to the cataract extraction data we've already shared, the incidence of secondary surgical interventions was similar for both the one-year Toric ICL and the five-year Myopic ICL study. Repositioning was .5 versus .8%. Replacement or removal was 1.9 versus 1.7%. And repair of retinal attachment was .5 versus .6%.

In the Toric ICL study, there were only six surgical interventions, for an incidence of 2.9%. Five were related to the device, and one was felt to be unrelated to the device. Of the five related events, one was removed due to a larger than expected vault with secondary enlarged pupil, but there were no other clinical symptoms.

One was removed due to elevated intraocular pressure associated with higher than expected vault.

One implant was placed primarily in the wrong meridian, which was recognized immediately and repositioned to the proper orientation three days postoperatively.

There was one patient who observed a photopsia immediately following the peripheral iridotomy and prior to the placement of the ICL. This

symptom remained after the ICL was implanted, and it persisted after the ICL was removed at the patient's request. It was felt that the photopsia was caused by the iridotomy and not specifically by the ICL.

And, lastly, one patient had a trace lens opacity at one week related to surgical trauma at the time of insertion. Although completely asymptomatic, the ICL was removed at the patient's request.

There was one event felt to be unrelated to the ICL. One patient developed a retinal detachment in one eye at nine months. Following correction of the retinal detachment and repair, this patient had 20/16 uncorrected visual acuity.

The safety profile observed in the clinical studies is further supported by postmarketing surveillance data from more than 296,000 implants collected between December 2005 and March 2013. Listed here are all the adverse events that have been reported to the Sponsor. The cumulative adverse event rate is 1.26%.

First of all, we recognize that underreporting of adverse events is common in clinical practice. However, specifically, for removals and replacements, we believe that this is an accurate and true reflection of the rate of occurrence. It is the policy of the Sponsor to provide a refund or replacement for any lens that is removed, thus creating a significant financial incentive for physicians to report this. In this global database, the overall rate of removal or replacement for any reason is 1.08%. This reflects all

potential causes, including sizing and power calculations.

Inflammation was assessed with the slit lamp using a standard scale. This graph represents data from a laser cell and flare substudy conducted as part of the Myopic ICL study. There is no evidence of any sustained inflammation over two years in any of these eyes implanted with the Myopic ICL. In the Toric ICL study, mild to moderate flare and cell resolved after the first week and remained absent after the first month visit in all patients. This is consistent with the findings of the Myopic ICL study.

Patient symptoms were assessed in both the Myopic ICL and Toric ICL studies using a subjective questionnaire administered at baseline and postoperatively. Patients were asked to rate the symptoms listed here as either absent, mild, moderate, marked, or severe. This graph represents the patient-reported symptoms rated as absent or mild in the Myopic ICL study. The vast majority of patients had either no or only mild symptoms, and there was no difference in any of the symptoms from preop to three years.

In the Myopic ICL study, there were a number of patients who reported moderate, marked, or severe preoperative symptoms. Following treatment with the Myopic ICL, there was no statistically significant change in any of these symptoms at three years.

A similar picture emerged from the Toric ICL study. The majority of patients reported either no symptoms or only mild symptoms,

and there was no difference in any of the symptoms from preop to 12 months. Similar to what was observed in the Myopic ICL, a minority of patients in the Toric ICL rated their baseline preoperative symptoms as moderate or severe. None of these differences were statistically significant between the preop and one-year visit.

Sizing and vault are directly related. The directions for use in the approved Myopic ICL recommend white-to-white measurement for ICL size selection but allow for the use of UBM or other technologies. In the image on the left, we see the white-to-white being measured with calipers. This is the current sizing method and most frequently used method worldwide, and this is the method that was used to guide lens size selection in the Toric ICL study. As you have seen, data from the Myopic ICL and Toric ICL studies demonstrated the overall complication rate is low using this method.

The Sponsor is committed to postmarketing studies of new technology that may improve the size and predictability, but in the meantime, the data presented here confirms an acceptably low overall rate of complications in the Myopic ICL and Toric ICL studies using white-to-white sizing.

The current Myopic ICL label as well as the Toric ICL protocol did not specify a vault range. In the Toric ICL study, 80% of eyes achieved a vault between 50 and 150% of corneal thickness, with a mean of 105%, with

excellent safety and effectiveness, as has been presented this morning. Based on these outcomes, the proposed directions for use recommend a 50 to 150% of corneal thickness vault as optimal. I'd like to clarify that this is a relative target value, and it's not intended to indicate the limits of what is clinically well tolerated.

But what about those eyes that did fall outside the targeted range? There are other factors, such as anterior chamber depth and anterior chamber angle that have to be considered. This slide details those eyes with vault outside the proposed recommended range at one month or later. The upper limit of acceptable vault is a function of the space consumed by the ICL relative to the space available in the anterior chamber. In eyes with deeper anterior chambers, a vault greater than 150% may be well tolerated.

In the Toric ICL study, there were 22 eyes with a vault greater than 150% of corneal thickness. The majority of those eyes had deep anterior chambers. In one case, the lens was removed due to excessive vault. The lower limit of vault may be determined primarily by the relative risk of anterior subcapsular cataract, but exactly where that lower limit lies is still a matter of debate.

In the Toric ICL study, 18 eyes had vault less than 50% of corneal thickness at one month or later. Three of those eyes had trace or greater opacity at 12 months.

So, in summary, when we compare the safety profile of the

Toric ICL at one year with the Myopic ICL at five years, we see a very similar safety picture. They are virtually identical in every category. And I wish to emphasize that the Toric ICL's safety profile exceeds all of the targets in draft guidance at the time of the study. Overall, these data show that the safety profile of the Toric ICL is consistent with the safety profile of the approved parent lens, the Myopic ICL.

All of the primary safety endpoints observed with the Toric ICL were better or comparable to those previously reported with the approved Myopic ICL. The safety of the Toric ICL has been established across a full range of myopia and astigmatism. This is further confirmed with global safety experience in nearly 300,000 eyes worldwide.

I'd like to now turn the podium over to Dr. Frank Price, who will discuss the Sponsor's data on endothelial cell loss and provide his clinical perspectives on the data you have seen here today.

Dr. Price?

DR. PRICE: Thank you, John.

My name is Francis Price. I'm a practicing corneal surgeon. As background, I do about 1% of all the corneal transplants in the United States, and I've helped pioneer new techniques to improve patient safety and outcomes for both corneal transplants and to treat complications of intraocular lenses. I am a paid consultant to STAAR Surgical. And I'd like to conclude the Sponsor presentation by reviewing the data on endothelial cell

loss from the original Myopic ICL post-approval study and offering my clinical perspectives on the data you've seen today.

First, let me give you some history that's important when we talk about cell counts. We need to appreciate that the approved Toric ICL protocol did not include an assessment of endothelial cell counts. Therefore, all the data on this important issue comes from the Myopic ICL study, which was a three-year follow-up study.

The MICL study enrollment was conducted between 1998 and 2001, and endothelial cell counts were evaluated in a substudy of 159 eyes. Then in 2005, the FDA requested a post-approval study of endothelial cell counts out to five years for patients in the substudy. As a result, those patients participating in the substudy had to be brought back in and followed for at least five years.

It's also important to appreciate that in this post-approval study, when it was -- it was started anywhere from four to seven years after those patients were initially enrolled in the MICL study, or in other words, one to four years after they had finished the study. This made it challenging to get them back in for follow-up. And as a result, the length of follow-up was variable. And this'll show up on one of the slides.

Now, we have some people on the Panel who may not be familiar with what cell counts are and why they're important, and I'd like to briefly explain why endothelial cell counts are important. There's a picture

on this slide of what a cell count looks like. These cells do not reproduce or divide after early childhood, and they are important to keep the cornea clear. The cell counts help us to make sure there are no short-term or long-term damage to these cells that could lead to corneas decompensating or turning cloudy.

A central reading center at Emory University with a mask reader was used to do all the cell counts for consistency.

As I mentioned, 159 eyes were followed for at least five years, and the average follow-up was 5.5 years. In fact, some eyes were examined more than seven years after surgery. In the overall cohort, the cumulative mean endothelial cell loss was 2.4% per year over 5+ years. In general, there is nothing to indicate a pathologic mechanism of endothelial cell loss in this population. You can look at the percent hexagonal cells and coefficient of variation, and these were comparable to normalized with no indication of chronic endothelial stress, as can be seen in pseudophakic bullous keratopathy, diabetes, and contact lens wear.

Shown here is a scatter plot of the actual endothelial cell densities for all 159 eyes over the 5+ years of follow-up, with a fitted regression line showing the average rate of cell loss. The regression was fitted to the data using a doubly repeated measures model.

Now, looking at this scatter plot, there's four key things I think you need to observe. As you can see, there was a wide range of preoperative

cell counts ranging from a minimum of 1900 to almost 3500. And this looks like a bell-shaped curve, more dense in the center. Remember, these lower preop cell counts were before the ANSI standards were formulated, and now we wouldn't have any cell counts below 2400.

During the first two to three years, you see a tight placement of exams, with the bars of the study exams in a row. But later on, the data is more scattered as the patients were called back for the post-approval study after they had exited the MICL study. And as I stated, some of those patients had actually reached seven- to eight-year postop times.

The overall population exhibits minimal cell loss. And, lastly, there were four eyes with fairly low cell counts to three-month exam. These eyes had acute cell loss after surgery without any further decline thereafter. And one eye had acute cell loss after a traumatic injury, which showed up at the one-year exam.

Now, overall, the data from the Myopic ICL post-approval study are consistent with data in the literature from eight cohort studies evaluating endothelial cell counts following implantation of ICLs. These studies were identified in the FDA's Executive Summary as providing relevant data on this topic, and they show a range of 2% to 12% cell loss. The median follow-up is three years and ranged from one to five years. The black line on the photograph shows the Myopic ICL data from the PAS, which represents the single cohort with the longest follow-up and the lowest preoperative cell

counts. Most importantly, there have been no cases of non-traumatic corneal decompensation or corneal edema that have been reported worldwide in patients implanted with an ICL.

As you may be aware, there were 10 eyes of 7 patients in the MICL study that were considered outliers, representing 6% of eyes with data. These eyes are considered outliers because they had accelerated cell loss compared with the overall cohort. They were greater than three standard deviations from the mean. Their cumulative cell loss was more than 30% from baseline after four to six years.

Now, at this time, the etiology of that accelerated endothelial cell loss has not been determined. However, STAAR has continued to follow those patients out to 10 years and beyond. And the good news is that their rate of cell loss has slowed and actually appears to have leveled off with longer follow-up.

In addition to these 10 eyes, 2 eyes had low cell counts at the one-year exam, but we do not have preoperative cell counts on those eyes, and 4 eyes had surgical trauma, as I showed you previously.

Now, shown here are data out to eight years, and the 10 outlier eyes are represented with red triangles. As you can see, the regression line for the mean cell loss in those 10 outliers is steeper than the regression line for the remainder of the cohort.

I'd like to tell you that we know why those 10 eyes had such

rapid cell loss, but we don't. Shown here is a list of all the factors that we have analyzed, and we found no definitive association with endothelial cell loss. These factors include abnormal pigment dispersion, age, anatomy of the eye, and any clinical signs of inflammation, characteristics of the lens, including vault, IOP, degree of myopia, and other factors. However, one factor that we cannot rule out is potential effects of the laser iridotomy, which everyone in the study received. In fact, there is substantial evidence in the literature to suggest that iridotomies can lead to rapid endothelial cell loss in a small subset of patients. However, I want to emphasize we have no evidence that the iridotomy is a factor in these 10 eyes.

Now, when we look further to cell counts in these 10 outlier eyes, we can break them down into the original PAS study follow-up period and subsequent longer follow-up. And if you look at these two ones, you can see that the rate is slowed with longer follow-up. During the first 5+ years of that study, the rate was 5.9% per year, and the rate slowed to 3.7% per year when we reassessed the outliers out to approximately 11 years. And outside the study and not submitted to the FDA, we now have data on three of those outliers to 15 years of follow-up. It appears that the rate has continued to level off, with very little cell loss over the past four years.

Now, let me switch gears for just a moment and talk about the normal pattern of cell loss that we typically see in humans. And, normally, we see a bi-exponential pattern of endothelial cell loss over time. Bi-

exponential simply means there are two separate exponential loss functions, one steep and another less steep, and I'll show you these in a moment. And we typically see the same pattern of cell loss after nonrecurring trauma to the endothelium as a result of cataract surgery or corneal transplants. The rate of loss is initially fairly rapid, but the rate of loss slows and stabilizes over time unless there is ongoing chronic inflammation or trauma. Notably, as Dr. Vukich showed you, there is no evidence of ongoing inflammation in patients implanted with the Toric ICL.

Now, this graph shows the bi-exponential pattern of cell loss with age. The rate's very rapid until about 10 years of age, and then it begins to slow and stabilizes as we reach adulthood.

As I mentioned, a similar pattern is typically seen after cataract surgery, where we have a rapid cell loss that then stabilizes later. And on this graph, the scale is in months, not years.

And, finally, here is data after corneal transplants showing a very similar bi-exponential pattern, which varies depending upon the amount of initial surgical loss.

So as we consider implants like the Toric ICL, we would like to know about the long-term trend and whether there is a potential problem looming. As I discussed, many types of ocular surgery can cause short-term acute endothelial loss. But the critical question is what is the rate of loss after cell counts restabilize? That is to say, after the acute cell loss from the

surgery has resolved, what is the ongoing rate, and is it higher than what we would expect? Please note this analysis I'm showing here has not yet been submitted or reviewed by the FDA.

So if we go back to the Myopic ICL post-approval study, what is the pattern we see? As shown by the red curve, the pattern we see here is similar to what we expect after cataract surgery. We can fit a similar bi-exponential equation to these data. The acute cell loss resolved after about three months, and thereafter, the rate of cell loss is much more gradual. The initial cell loss with surgery, I think, is technique or surgeon-dependent, and this can be modified with experience and improved techniques. After three months, we estimate that the rate of cell loss slows to about 2% per year. And this indicates to me that the ICL is safe for the cornea.

To summarize, what I've shown you is that the main cohort in the Myopic ICL post-approval study followed a bi-exponential pattern of cell loss similar to what one expects after cataract surgery. However, a small group of outliers was identified that had greater cell loss and took longer than normal to stabilize.

In addition to the data from the Myopic ICL study, I'd like to share some postmarketing data on corneal edema and put these MDRs in perspective. In the period from approval of the Myopic ICL in December of 2005 through May of 2013, more than 200,000 Myopic ICLs were implanted. Those surgeries were associated with 30 reports of corneal edema and one

report of an explant due to endothelial cell loss. All the corneal edemas appear to have been acute events related to the surgery. More than half were reported within one week of surgery, and nearly all within the first year. And the incidence of these events is quite low, as you can see, where it's 0.02%.

Now, let me summarize what I've shown you with respect to endothelial cell loss. First, it's important to keep in mind that approximately 400,000 total ICLs have been implanted over the last 17 years, and there have been no reports of non-traumatic corneal decompensation. Secondly, the data from the MICL post-approval study are consistent with the literature. And for those 10 outlier eyes that had greater cell loss and took longer than normal to stabilize, we have not been able to determine a mechanism or medical reason to explain the observation. However, we do know there's no clinical evidence of ongoing inflammation.

Now, let me wrap up with a brief summary of the overall data from the Toric ICL study, and I'll share with you my clinical perspectives on the data. As a reminder, the sensitivity analyses have not yet been submitted or reviewed by the FDA.

We've heard a lot today about the integrity of the clinical trial and concerns about the study methods and conduct. We need to keep in mind this study was designed in 2001 and initiated in 2002. At that time, the methods of measuring postoperative axis alignment were not as

sophisticated as they are today. And although there were protocol deviations, they were unlikely to have affected the study outcomes, as demonstrated by the multiple sensitivity analyses. Therefore, I think the data can be trusted.

So why do we need the Toric ICL? Clearly, there is a significant unmet need for additional treatment options for myopic astigmatism, particularly for patients who are unsatisfied with glasses or contacts and may not be candidates for laser or incisional procedures. The beauty of the Toric ICL is that it corrects both myopia and astigmatism with a single procedure and eliminates the need for a secondary procedure to correct astigmatism.

The Toric ICL study had impressive visual results, and these visual results have to do with basic optics. For a 10-diopter myope, there's a 20% increase in image size with an intraocular lens correction versus a glasses correction at 12 mm in front of the eye, as well as decreased distortions.

As I review the safety and effectiveness outcomes, I want you to remember just one number, 77%. 77% of patients in the Toric ICL study had uncorrected visual acuity at 12 months that was equal to or better than their best-corrected vision after surgery. For those of you who aren't in eye care, that means that without glasses, after surgery, 77% of the people were able to see as well or better than they did with their glasses before surgery. In fact, 77% of patients also gained at least one line of best-corrected vision

compared to their preoperative best-corrected vision. And very few patients lost one or more lines of best-corrected vision. It is quite impressive to see the distribution in these histograms, shifting the bell-shaped curve to the right, with an overall improvement in best-corrected visual acuity.

And, finally, the refractive outcomes in terms of both manifest refractive spherical equivalent and manifest cylinder remain very stable over time. And this supports the conclusion that the lens is rotationally stable. Thus, the Toric ICL, like the Myopic ICL, has unrivaled effectiveness in terms of treating moderate to high myopia, with equally effective correction of astigmatism and good rotational stability.

In summary, we have shown you that the postoperative visual acuity outcomes with the Toric ICL met or exceeded all established targets and were better than the Myopic ICL data. And the Toric ICL is associated with excellent patient satisfaction. The potential risks are well characterized and comparable to any intraocular lens, as demonstrated by postmarketing experience in more than 400,000 implants over 17 years. Of those, more than 38,000 ICLs have been implanted for 10 years or longer and more than 9,000 for 15 years or longer.

This favorable safety profile was confirmed in the Toric ICL study, which demonstrated good preservation of best-corrected visual acuity and a low incidence of complications and adverse events.

And, finally, as you heard from Barry Caldwell, STAAR Surgical is

committed to further characterizing the long-term safety profile of the ICL platform.

Thank you for your attention, and now we'd like to address your questions.

DR. HIGGINBOTHAM: This is Dr. Eve Higginbotham. I would like to thank the Sponsor's representatives for their presentation. We now have about 20 minutes for a question and answer period, and I would invite the Sponsor to the table to facilitate the question and answer period.

Does any member of the Panel have a brief clarifying question for the Sponsor? Please remember, Panel, that you may be able to ask additional questions during the Panel Deliberations session this afternoon, so you don't have to ask all of your questions now.

Dr. Weiss?

DR. WEISS: I had a question, just a few questions of clarification. One is for the improvement of visual acuity, there were almost double from 41 to 77% of people who could see 20/16 after the lens uncorrected than could see it before. I'm curious how the visual acuities were obtained. Were these double-blind, or was the examiner aware of what the patient was having done, in which case it would be very possible to push the patient a little bit more after the procedure to see a better line of vision?

MR. HUGHES: These were not double-blind.

Dr. Schallhorn, do you want to comment?

DR. SCHALLHORN: Well, they weren't masked to that effect. But I think the --

DR. HIGGINBOTHAM: Please state your name.

DR. SCHALLHORN: I'm sorry, yeah, Dr. Schallhorn. The observers were not masked when they measured the visual acuity, and undoubtedly some of the improvement in visual acuity was because of the reduction in minification effect also. But I think, really, when you look at the data, overall, there was clearly an improvement in both uncorrected and best-corrected vision.

DR. WEISS: Okay. I also had a question in terms of surgical reinterventions. You showed us the data comparing surgical reintervention from the one-year for the toric versus the five-year. There was a 2.4% at the one-year, but what was the -- I'd like to compare apples and apples. What was the surgical reintervention rate for the toric versus the standard lens at one year, at the same time point?

MR. HUGHES: Dr. Vukich?

DR. VUKICH: Let's see here --

DR. HIGGINBOTHAM: Please state your name, Dr. Vukich?

DR. VUKICH: I'm sorry. Dr. John Vukich. We have the data segregated by the five years. We felt that was more complete and would give a fuller counting of the interventions. I don't believe we have the one-year slide prepared but could have that for the deliberations, and we'll get

that data for you.

DR. WEISS: Because as time goes on, you would expect more interventions rather than less, so --

DR. VUKICH: Correct.

DR. WEISS: -- than if you had the same amount. So if you had that later, that would be great.

And the last question I had was the sensitivity analysis is going to be -- is very important to try to sort of compensate or understand all the protocol deviations, and also, as a Panel member, we're going to be asked is this valid scientific evidence. So I was curious why such important data wasn't submitted to the FDA, because that's going to be very important to analyze.

MR. HUGHES: Well, this --

DR. HIGGINBOTHAM: Please state your name.

MR. HUGHES: I'm sorry. Robin Hughes. This analysis has been ongoing, and we have not had a chance to submit it to the Agency at this point.

DR. WEISS: Thank you.

MR. HUGHES: Many of the protocol deviations were discovered late in the process, so we haven't had a chance to give them a timely submission.

DR. WEISS: Okay. Thank you.

DR. SCHALLHORN: If I could just -- Dr. Schallhorn. Again, if I could just add one thing, and that is it will definitely be submitted, so there's every intention of submitting this. I think you're right. It is important data. It's critical data for the Agency to review, and it will be submitted.

DR. HIGGINBOTHAM: Dr. Glasser?

DR. GLASSER: David Glasser. Dr. Price, I have a question about the endothelial cell data you presented. You showed a bi-exponential loss, with an increase during the first three months and then a stabilization after that. Were you able to look at the longer term data to see if that cell loss between one year and five to eight years remained the same, or was there a further decrease in cell loss percentage in the out years?

DR. PRICE: This is Dr. Price. I'm not sure I understand your question.

DR. GLASSER: I'll try again.

DR. PRICE: Do you want to know about the PAS study or the outliers?

DR. GLASSER: In the PAS study, not the outliers.

DR. PRICE: All right.

DR. GLASSER: The larger group of non-outliers, did the cell loss decrease from one year to five years to eight years, or did it remain the same in the out years?

DR. PRICE: That's a very good question. I'm not sure I can

answer that exactly. We do know that it fit the bi-exponential pattern when we tried that, and that would indicate that it does level off some with time, but we'll have to get back and check that for you.

DR. HIGGINBOTHAM: Dr. Macsai?

DR. MACSAI-KAPLAN: Thank you for presenting your data. I would echo Dr. Weiss's request for some sensitivity data. It would be very helpful in our analysis.

Regarding the change in visual acuity and the loss of minimization, I noted that you used best spectacle-corrected visual acuity preoperatively and compared it to postop vision. Did you have best contact lens corrected visual acuity, because that might be a more valid comparison?

DR. VUKICH: Entry criteria was -- I'm sorry -- Dr. John Vukich. Entry criteria was best spectacle-corrected visual acuity. And, in fact, for the Toric study, the patients were taken out of their contact lenses for a period of time prior to the entry exam so that we do not have that comparator.

DR. MACSAI-KAPLAN: I think that would be important information regarding any labeling or any claims made by the Sponsor.

Second of all, since this device is different from the MICL in that the curvature or the toric is on the anterior curvature, the change of the MICL is on the anterior curvature to get the toric effect, how does that effect pigment dispersion and the iris laying on the ICL? Was there a measurement of pigment dispersion? Was gonioscopy done to look at pigment in the angle,

et cetera?

DR. VUKICH: Dr. Vukich. Gonioscopy was not a part of the Toric ICL study. This was an efficacy study that was designed to supplement the safety study of the parent lens. And so that parameter, as well as other factors like endothelial cell counts, were not part of the toric lens but were based on the predicate lens, the Myopic ICL.

DR. MACSAI-KAPLAN: Can you clarify for me if the laying of the iris on the anterior surface of this device is different from that seen in the MICL?

DR. VUKICH: Dr. John Vukich. The toric surface is on the anterior surface of the lens. This is a relatively small change in the shape profile across a small optic. It is measured in microns of difference from one edge to the other in terms of the physical parameters. And, again, we don't have data on gonioscopy or how the iris would interact with that small change in the lens. But we believe it is -- we know it is minimal and on the order of microns of difference to create a toric surface versus a spherical surface.

MR. HUGHES: This is Robin Hughes. If I could just build on that, the edge thickness on the toric lens, on the toric curvature, is actually thinner than the edge thickness on the MICL, so there should be less interaction.

I'd like to introduce Dr. Rob Rivera. He also wants to come up.

DR. RIVERA: Dr. Rob Rivera. We clinically see no difference between the Toric ICL and the Myopic. In clinical practice, we've gone back and looked with Visante OCTs, and you literally can't tell any difference either with a Visante scan or, you know, on your slit lamp exam either. So they look very much -- very similar.

DR. HIGGINBOTHAM: Dr. Weiss?

DR. WEISS: Just trying to understand some of the denominators. So we got down to the 194 that we were looking at for most of the results. For the absolute cylinder, the *n* was 167. So I was wondering why the difference. That was slide 39, page 20, if you need -- so the denominator on that particular slide is 167, so I'm just --

UNIDENTIFIED SPEAKER: (Off microphone) What was that number?

DR. WEISS: It was slide 39, page 20, but I have to -- let's see -- and it was discussing the absolute cylinder.

MR. HUGHES: I'd like to introduce John Santos.

DR. SANTOS: John Santos, STAAR Surgical. That different denominator is based upon patients available at the two visits, both the 6 and 12 months. It's a paired analysis.

DR. WEISS: But I thought in some other things there were more patients available at the six-month. Did you always have 167 available at the six months, or it was only for some things you had 167, for other things

you had more patients?

DR. SANTOS: There would be more patients at six months, but maybe they weren't available at 12, so for the paired analysis, there were 167.

DR. WEISS: Okay.

DR. HIGGINBOTHAM: Did that answer your question, Dr. Weiss?

DR. WEISS: Yes, it did. And I had another quick follow-up. In terms of the secondary surgical interventions, again, on page 7 in the Ophthalmic Devices Panel Executive Summary, it has Table 1 of adverse events. It has the ISO rate percentage to compare, which is .8%, where the surgical reintervention ended up being triple that. I assume we really shouldn't be looking at that .8% because that would suggest that the surgical reintervention was much too high. So could you help me understand the ISO rate percentage, which is used as a comparison of what one would expect? How does that fit into the actual surgical reintervention rate for the TICL?

DR. VUKICH: This is Dr. John Vukich. This is a slide that goes over the cumulative complications of adverse events, and we are looking at, then, the comparators for the ISO rates. The ISO rates are based on a sample of 300. We had 210 to work with. The surgical reinterventions, of which there were five in this study, did have a rate of 2.4%, and that is greater than the .8%. We went over in detail on each of these patients during the

presentation, and this does exceed the ISO rate, but we don't believe that it is directly applicable in terms of the ISO rate. I don't believe that was involved specifically for either phakic IOLs.

DR. WEISS: So to understand it better, because this is going to be consideration --

DR. VUKICH: Sure.

DR. WEISS: -- for something that overshoots a rate that the Sponsor is giving us, would you say at this point you don't -- and I think you did -- that the ISO rate doesn't really apply to this type of IOL? Or just I want to understand it a little bit better in the context of how to evaluate that higher number.

DR. VUKICH: John Vukich. Within the context, the ISO rate was not specifically developed for phakic IOLs, and so we believe that this is not directly applicable. Listed here are the five patients in which there was a secondary intervention. And we can see the resolution of these as well. One of them was a retinal detachment, and we think that's just part of being highly myopic and has nothing to do with the lens itself. Misalignment, one of the cases. That I think is just a teaching issue, and we'll get better and have gotten better at teaching, so I think we can look at some of these as being things that can be mitigated, again, with further experience and with clinical training.

DR. WEISS: And then just a quick question. In terms of the

review of the global literature, because there has been a lot of experience with this, what is the standard reop rate in the TICL and other outside of this study?

DR. VUKICH: Dr. John Vukich. The global literature, of course, is going to be looking at various different subpopulations, different ethnicities, and different *n* values; from the 43 publications that the Agency observed, they did a pretty careful analysis, and we have the MDR data as well. We think that one that we are very confident in is the removals and exchanges rate that is reported to the company just based on this huge incentive that patients have -- or that doctors have to report that event. And it's 1% removals and exchanges. If we look at the global safety experience as reported in the MDR, these are the reports of the various encounters. They are listed only once even though more than one of these items could occur for any one patient, so that they add up and cumulatively add up to 1.26%.

DR. WEISS: So the surgical removal would be actually a subset of surgical intervention. So are there any articles, even if it's a different population, that talk about their experience and include what their secondary surgical interventions are even if it is a different population?

DR. VUKICH: There are articles that address both results, safety and efficacy, of this, and in summary form, we can present that, but I do not have a prepared slide --

DR. WEISS: Yeah, I mean, if you don't have it available, maybe

after the break --

DR. VUKICH: We don't have a prepared slide --

DR. WEISS: -- you know?

DR. VUKICH: Yeah.

DR. WEISS: Okay. Thank you very much.

DR. HIGGINBOTHAM: Dr. Eydelman?

DR. EYDELMAN: Yes, hi. I just wanted to add to what Dr. Vukich just stated. Dr. Vukich is correct in that the original IOL grid intervention rate was not put together with phakic IOLs. Having said that, the ISO was just revised and finalized for all IOLs, including phakic, and it does still have .8 as the rate for reference for secondary interventions.

DR. HIGGINBOTHAM: Dr. Huang?

DR. HUANG: Yes, I have -- I was wondering if -- that in your -- there were 54 measured data point deviation from the protocol out of this 194 patient. So are those 54 points entered into your analysis, or those are excluded from the analysis?

MR. HUGHES: Dr. Schallhorn?

DR. SCHALLHORN: This is Dr. Schallhorn. Those ones I discussed were included in the analysis. Specifically, the lens outside of the protocol for sphere and cylinder, the ones that were outside of protocol because of the axis target, and for lens length. Those were included. As I mentioned, when you look at the type of deviation it is and the low likelihood

that it would affect outcomes and the sensitivity analysis, we felt it was prudent to include those in the analysis.

DR. HUANG: Did the exclusion or inclusion of those data -- will affect your sensitivity or specificity?

DR. SCHALLHORN: This is Dr. Schallhorn again. Yes, they -- well, let me say that we did look at that in the sensitivity analysis, and including or excluding those did not affect the outcomes.

DR. HIGGINBOTHAM: Yes, Dr. Huang, one more question?

DR. HUANG: In terms of -- this is probably direct -- and this is Andrew Huang -- I direct to Dr. Frank Price. In terms of those outliers with significant endothelial loss, I was wondering if the Sponsor has looked into if the size or the power or, you know, the preoperative condition the patients have, maybe higher myopia or lower myopia, you know, causes a significant loss of endothelial density?

DR. PRICE: Dr. Huang, that's an excellent question. All of those have been looked at. We can put this slide up. These are all the -- here it comes -- these are all the items that the Sponsor looked at, and none of these correlated or appeared to have any relationship with these 10 outliers. So at this point, we don't really have an explanation, and it's an ongoing issue with the company that they're continuing to try to find out what that could be.

DR. HIGGINBOTHAM: Did that answer your question, Dr. Huang?

DR. HUANG: Just a quick follow-up? I was wondering -- thank you very much. This is Andrew Huang. Because of the data, I know the population is only about 210, but I was wondering if it's possible to stratify the patient profiles, such as the implant power and the preop myopia, to find out, you know, if the endothelial decrease is different among the subgroups.

DR. PRICE: This is Dr. Francis Price again. All the data is from the myopic study. So it's 159 that was a subset of the myopic study. None of this data is from the toric study. And they did look at lens power. They looked at the amount of myopia preoperatively, and none of that correlated, or the length of the lens. None of this correlated with the cell loss. So they looked at all the aspects of the lens, all the preoperative surgical data, interventions for surgery, and none of those correlated in these 10 eyes that had the increased cell loss over the first few years after surgery.

Does that answer your question?

DR. HUANG: Thank you.

DR. HIGGINBOTHAM: Dr. Coleman, you have the last question.

DR. COLEMAN: Yes, this is Dr. Coleman. And my question is, is what was the average amount of time that those late out-of-window visits were and the range?

DR. SCHALLHORN: This is Dr. Schallhorn. The average amount was a little bit less than three months late, little bit less than three months late, and I believe it went out to -- well, in fact, hang on for one sec. Let me --

it's right here if we can get this slide up.

So here is the -- this is the distribution of the out-of-window visits, the ones that are early and the ones that are late, and you can see the distribution just ranked by how late or how early they were. Now, almost all of the early visits were seen concurrent with a timely primary eye. And you can see that most of the late visits were from one site, and that was the Navy site, NRSC, on this slide. Again, the reason for the late visits at that site was unexpected deployment of these active-duty folks.

DR. HIGGINBOTHAM: Dr. Macsai, you want to ask your question now, or would you like to --

DR. MACSAI-KAPLAN: Do we have time?

DR. HIGGINBOTHAM: Yes.

DR. MACSAI-KAPLAN: My question had to do back with Dr. Huang's anterior chamber depth and the endothelial cell count. In this protocol, you talk about an anterior chamber depth of 2.8. What is the lowest acceptable anterior chamber depth? Because I thought the MICL was not approved for 2.8 anterior chamber depth.

MR. HUGHES: Dr. Vukich?

DR. VUKICH: Dr. John Vukich. This study was initiated during the conclusion of the Myopic ICL study and prior to the labeling and approved use of the MICL. And so the 2.8 number was used originally in both protocols, the Myopic ICL as well as the Toric ICL, and hence, those were

consistent in terms of the enrollment criteria for these patients. And, subsequently, when this was approved by the Agency, it was then truncated at the 3.0 mm.

DR. MACSAI-KAPLAN: So when you looked at the endothelial cell loss rate, did you segregate the groups, not just looking for an association of one factor versus another, but did you actually segregate the groups based on anterior chamber depth?

DR. VUKICH: This is John Vukich. We have looked at a number of factors, including anterior chamber depth. Of course, there could be some proximity issue we'd look at, the peripheral iridotomy size and location, the power of the implant. These are all factors in which we looked for a correlation and were unable to find anything definitive. Understanding there are only 10 eyes in which this is an accelerated loss, perhaps the number may not reveal an association clearly.

DR. HIGGINBOTHAM: Did that answer your questions, Dr. Macsai? Yes?

Dr. Chamberlain?

DR. CHAMBERLAIN: Winston Chamberlain. Three brief questions. One is just relating to the endothelial cell loss again. The small 159 in the MICL-PAS, any way to stratify endothelial cell loss based on age? Or was that done? I wasn't clear if you said that.

DR. PRICE: This is Dr. Price. I'm not sure it's been stratified for

age for the entire group, but for the 10 outliers, age was not a factor. It was one of the items that they looked at.

DR. CHAMBERLAIN: The thought there just being is there a age-related activity in terms of, you know, agitation of the lens, pigment dispersion, that kind of thing?

And related to that, are surgeons who are putting these in and doing the postop exams, are they noting iris transillumination defects or changes in pupillary size postoperatively? And is that measured in any sort of a standardized fashion?

DR. VUKICH: Dr. John Vukich, pupil roundness or out of roundness and transilluminations were recorded in the Myopic ICL study, again, the parent study in which we were looking at safety as well as efficacy. There was the ability to note unusual findings in the toric study, but not being designed or powered for safety, we didn't specifically look for those things.

DR. RIVERA: Dr. Rob Rivera. Just one comment on the outliers. One patient, in both eyes, one patient of the seven actually did have one identifiable cause for trauma, which was multiple traumatic events postoperatively, including orbital bone fractures. So that's the only patient in whom we could have said this is, you know, one key factor.

And as to the question about transillumination defects, we don't see any; actually, we don't see any at all. In fact, quite a number of patients have now had the ICL long enough that they have entered into the

cataract age range, and upon removing one of these, you know, 15-year-old ICLs, we find that the not only is the iris acting normally upon its removal and the subsequent cataract surgery, but the ICL on removal has no synechia. There's no pigmentary deposition on it that you could say is the result of any adhesion, and they do remove very easily. So it's not really stuck, as such, and there's not really an abrasive effect that we're seeing to create transillumination defects.

DR. HIGGINBOTHAM: Thank you. We are now going to take a 17-minute break. It is now 10:18.

Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any member of the audience. I'd like to remind everyone we have more than one set of bathrooms, or restrooms. There is one set down this hallway and then around the corner past the reception desk. We will resume at 10:35.

(Off the record.)

(On the record.)

DR. HIGGINBOTHAM: This is Dr. Eve Higginbotham. It is now 10:35. I would like to call this meeting back to order.

FDA will now give their presentation. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

FDA will also have 100 minutes to present. FDA, you may now begin your presentation.

DR. NGUYEN: Good morning. My name is Tieuvi Nguyen, and I'm a biomedical engineer in the Division of Ophthalmic and Ear, Nose and Throat Devices. I am the Team Leader for the subject PMA for the STAAR Surgical Visian Toric Implantable Collamer Lens.

There have been many FDA reviewers that have been involved with this application since its initial submission. This slide represents the review team for the most current amendment.

First, I will be providing a brief overview of the regulations of intraocular lenses. Monofocal IOLs are lenses with a single focus that are intended to treat aphakia, which is defined as the absence of the natural lens due to surgical removal. Most patients that undergo cataract surgery are implanted with a monofocal IOL.

Premium IOLs are new types of IOLs that are intended to provide benefits beyond treating aphakia. These include multifocal, toric, accommodating, and phakic IOLs. Currently, about 13% of patients are implanted with premium IOLs. All IOLs are Class III medical devices and require premarket approval.

Phakic IOLs are implanted into the eye only to reduce a person's need for glasses or contact lenses. Phakic refers to the fact that the lens is implanted without removing the eye's natural lens. There are

currently approved PMAs for two phakic IOLs. It should be noted that one of the currently approved phakic IOLs is STAAR Surgical's Visian Implantable Collamer Lens for myopia, also referred to as the MICL. The device that will be discussed at today's meeting is a modification of the MICL.

Toric IOLs are intended to correct cylindrical in addition to spherical error in eyes with astigmatism. Astigmatism is an optical defect in which refractive power is not the same in all meridians. Treatment options available to patients with astigmatism include eyeglasses, contact lenses, laser refractive surgery, and IOLs. There are four toric IOLs that are currently approved for use in the U.S.

FDA has been working with the American National Standards Institute and the International Standards Organization since the 1980s to develop ophthalmic standards in these three categories: ophthalmic implants, contact lenses and care products, and ophthalmic instruments. An FDA-recognized standard is a consensus standard that FDA has evaluated and recognized for use in satisfying a regulatory requirement and for which FDA has published a notice in the Federal Register. There are 36 recognized ophthalmic standards.

There is currently one toric IOL standard that has been published and is awaiting FDA recognition, ANSI Z80.30. There is an ISO toric IOL standard under development which will be incorporated into the revised ISO 11979-7 standard.

The Visian Toric Implantable Collamer Lens is a phakic IOL that is placed in the posterior chamber of the eye directly behind the iris and in front of the anterior capsular of the crystalline lens, as shown in this figure. As previously stated, the Visian TICL is a modification to the applicant's currently approved MICL. The major difference between the proposed TICL and the currently approved MICL is the incorporation of a toric surface on the anterior side of the optic. Like the MICL, the TICL is designed as a single piece plate haptic. It is made of a proprietary collamer polymer material, and the optical zone incorporates a forward vault to minimize contact with the central anterior capsule.

The applicant developed a calculator software as part of their device to provide surgeons the ability to select a lens that provides the expected postoperative refraction closest to the surgeon's desired postoperative refraction. The calculator outputs are recommended TICL cylinder power and a range of sphere powers using preoperative keratometry, manifest refraction, anterior chamber depth, and corneal thickness inputs entered by the surgeon.

STAAR has proposed the following indications for use: The Visian TICL is indicated for use in adults 21 to 45 years of age for the correction of myopic astigmatism in adults with spherical equivalent ranging from -3 to less than or equal to -15 diopter; with cylinder of 1 to 4 diopters for the reduction of myopic astigmatism in adults with spherical equivalent

ranging from greater than -15 to -20 diopter with cylinder 1 to 4 diopter; with an anterior chamber depth of 3 mm or greater when measured from the corneal endothelium to the anterior surface of the crystalline lens and a stable refractive history (within .5 diopter for one year prior to implantation); the Visian TICL is intended for placement in the posterior chamber (ciliary sulcus) of the phakic eye.

As previously stated, there are only two phakic IOLs currently approved in the U.S. These lenses are approved only for the correction of spherical error. Currently, there is no approved phakic IOL available in the U.S. for the correction of astigmatism. Hence, the device being brought for Panel consideration today is considered a first-of-a-kind.

Now I will discuss the regulatory history of the applicant's submission for the TICL. This history is relevant because of the length of time associated with the data collection and review and the changing clinical landscape associated with this technology.

The MICL was the platform for the design of the TICL lens and was approved on December 22nd, 2005. Prior to the MICL approval, the applicant received approval on January 3rd, 2002 to initiate a clinical trial for the TICL lens.

Following the initiation of the trial, FDA conducted an inspection of the applicant's U.S. site. The purpose of the inspection was to ensure that the data and information contained in the IDE submission were

scientifically valid and accurate. Due to a number of objectionable conditions observed during the inspection, the applicant was issued a warning letter. This warning letter cited a number of issues, including the applicant's failure to obtain FDA approval prior to initiating a study, failure to ensure a continuing IRB review and approval, failure to obtain signed investigator agreements from participating investigators, and failure to provide investigators with adequate information required to perform the study.

On May 17th, 2004, STAAR provided FDA with the steps that have been taken and the ones that were ongoing to correct these violations and to prevent the occurrence of similar violations in current and future studies.

The applicant submitted their PMA for the TICL on May 8th, 2006. Following review of the application, the applicant was issued a major deficiency letter. Some of the major issues identified in the deficiency letter include, but were not limited to, inadequate analyses to demonstrate the effectiveness of the device for the different cylinder powers, uncertainties regarding the labeled TICL, the lack of reporting of protocol violations, the inadequacy of the applicant's analysis of subject accountability, and new safety concerns that were raised as a result of new medical device reports that were reported at the time for the MICL lens. Note that the TICL IDE study was not designed to demonstrate safety of the lens as the applicant was relying primarily on the established safety of the approved MICL.

Additional information regarding this issue will be discussed later in FDA's presentation.

On February 15th, 2007, FDA conducted another inspection of the applicant's U.S. site to follow up on the corrective actions of the violations identified during the 2003 inspection. The inspection identified numerous issues and concerns regarding the quality of data submitted in support of the PMA, some of which were repeat violations from the 2003 inspection. As a result, the applicant was issued a second warning letter on June 26th, 2007.

This letter cited the applicant's failure to submit an IDE study for approval prior to initiation of the study and failure to ensure IRB review and approval were obtained. In addition, the applicant was also cited for a failure to ensure that all investigators complied with the approved investigational plan and applicable FDA regulations, failure to immediately conduct an evaluation of all unexpected adverse events, and failure to submit required reports and information to FDA. It should be noted that the first two categories of objectionable conditions were also cited in the first warning letter issued in 2004.

As a result of the findings of this inspection, the applicant was placed on a data integrity hold, which stopped the review of the PMA. At this time, FDA requested a third-party, independent audit of all the clinical data as well as a system audit. In addition, FDA requested that the applicant

provide a corrective action plan that would provide assurance that future submissions would contain accurate, complete, and verifiable data and information.

The independent third-party reports were provided to FDA on October 8th, 2008 and March 13th, 2009. STAAR provided their corrective action plan on May 22nd, 2009.

FDA reviewed the third-party reports CAPA and found them to be acceptable. Subsequently, the integrity hold was lifted, and the review of the applicant's PMA application continued.

STAAR received a second major deficiency letter for their PMA application on February 3rd, 2010. The deficiency letter identified new safety concerns based on endothelial cell loss data obtained from one of the MICL post-approval studies. As a reminder, the TICL study was relying on the MICL study data for safety. These concerns will be discussed later in FDA's presentation of the safety data and the post-approval study.

In addition to the safety concern, FDA requested that the applicant evaluate visual distortion for high astigmatism subjects to support the full range of requested cylinder powers. The letter also listed a number of concerns regarding the applicant's analysis of rotational stability.

Following receipt of the applicant's response to the second deficiency letter, an Advisory Panel meeting was scheduled for May 20th, 2011. However, during interactions with the applicant during Panel

preparations, it became apparent that data and analyses provided by the applicant in different communications were contradictory. The applicant explained to FDA that the discrepancy was due to the fact that some analyses were based on the pre-audit database while others were based on the modified database following the independent third-party audit.

Due to these inconsistencies, the Panel meeting was cancelled and the review of the PMA continued. The applicant was issued a not approvable letter for their PMA on November 22nd, 2011.

In addition to the inconsistencies in the databases, FDA also had concerns related to the study's low subject accountability, the large number of previously unreported protocol deviations, and the lack of adequate software and mechanical validation studies.

The applicant provided their response to the not approvable letter on November 16th, 2011. At this time, a second attempt was made to schedule an Advisory Panel meeting. However, similar to the events that occurred during the preparation of the first scheduled Panel meeting, interactions with the applicant during Panel preparation revealed a number of concerns.

The applicant informed FDA in June of 2013 that they had made unapproved changes to the design of their device sometime before 2004. Note that this was after the initiation of the IDE trial, which means that some subjects were implanted with a modified device while others were implanted

with the originally approved design. Interactions with the applicant also raised concerns regarding the inadequacy of the quality control processes and test equipment. In addition, during these interactions, the applicant also provided FDA with additional protocol deviations. However, it was unclear if these new protocol deviations were items that were identified from the third-party audit or if they were items that were not previously identified.

Due to these concerns and their significant impact on the interpretation of the clinical data, the Panel meeting was again cancelled. FDA continued interacting with the applicant to gain a better understanding of the data and its results. FDA also initiated two directed inspections of STAAR Surgical facilities in an attempt to clarify these issues.

On August 8th, 2013, FDA inspected STAAR's manufacturing facility to verify the manufacturing and quality control procedures. FDA also verified the applicant's qualification studies for the manufacturing of the TICL since 2002, which were not previously provided to FDA for review or for which the significance was not adequately described to FDA. During this inspection, FDA also attempted to identify which version of the device design each subject in the clinical trial received.

The inspection revealed that the applicant had not adequately maintained their device master record. They had also not adequately established procedures for corrective and preventative action and did not have adequate procedures established to control products that do not

conform to specified requirements. STAAR provided new data to the PMA in response to some of these observations. FDA notified the applicant that all corrective actions would be verified at the next routinely scheduled inspection.

This inspection was followed by a data inspection of STAAR's U.S. site to investigate specific items related to the conduct of the clinical study, such as the determination of protocol deviations and the evaluation of how protocol deviations were reported following the third-party audit. This inspection also investigated why there was such a large increase in the reporting of deviations during the review of the current amendment. There are no inspectional observations cited during this inspection. However, FDA discussed the following observations with the applicant.

It was noted that the applicant failed to validate the investigational lens selection software. They failed to amend their study protocol to specify the appropriate type of visual acuity testing that was to be used by each investigator. And the applicant was unable to provide evidence of training content for the investigation site personnel. FDA upgraded the inspection from no actions indicated to voluntary actions indicated due to the impact of these discussion items on the conduct of the study. FDA will follow up on the applicant's corrective actions to address these discussion points during the next routine inspection.

FDA continued to interact with the applicant following the

inspections to clarify these issues. On November 21st, 2013, the applicant was informed of FDA's decision to reschedule the Advisory Panel meeting.

Today we wish to solicit the Panel's opinion on the safety and effectiveness of this first-of-a-kind phakic toric lens. FDA's presentation today will summarize data from the pivotal IDE study for the toric ICL. The safety data will be presented by Dr. Maryam Mokhtarzadeh. The effectiveness data will be presented by Dr. Gene Hilmantel. And the Sponsor's proposed post-approval study will be presented by Dr. Youlin Qi.

Dr. Mokhtarzadeh will now present on the safety data for the TICL study.

DR. MOKHTARZADEH: Good morning, distinguished Panel members, STAAR Surgical representatives, FDA staff, and the public. I will be presenting to you this morning an overview of the study design and key safety results of the pivotal study submitted by the applicant in their premarket approval application for the STAAR Surgical Visian Toric Implantable Collamer Lens in addition to FDA's related questions for Panel consideration.

Available clinical data pertaining to the TICL lens platform includes the following: data from the MICL premarket application, data from the MICL post-approval studies, adverse events reported to FDA in medical device reports, literature, and data from the TICL premarket application. I will now describe each of these sources.

The pivotal trial for the MICL was a prospective, nonrandomized, multicenter, single arm study in which the primary control was the preoperative status of the treated eye. 526 eyes of 294 subjects were studied. A few key enrollment criteria are shown on the slide. As noted earlier, the MICL PMA received approval on December 22nd, 2005. The full summary of safety and effectiveness data can be seen at the web link shown on the slide.

The first condition of approval for the MICL PMA was extended follow-up of the MICL study cohort, continuing data collection on adverse events and endothelial cell density through five years postoperatively. The original MICL cohort consisted of 526 eyes. Of these, five-year or greater visit data was collected for 335 eyes. This study has been completed.

The final two conditions of approval were additional post-approval studies described on this slide. However, results from these studies will not be referenced in my presentation. Of note, the second post-approval study collects data on adverse events and complications, which would be relevant to my presentation on the safety of the ICL lens platform. However, final data will not be available until December 2018.

The FDA medical device reporting system is a nationwide passive surveillance system. Medical device reports, or MDRs, are received and entered into the Manufacturing and User facility Device Experience, or MAUDE database. The MAUDE database includes both mandatory and

voluntary reports.

The MDR system, while providing signals of actual and potential device related-problems, has some limitations. These include: (1) Underreporting of adverse events; (2) data quality issues since reports received are often incomplete; (3) it is impossible to determine incidence rates from MDR data alone; (4) reports received may not be representative and reflect a variety of reporting biases; and (5) root causes for reported events are often unable to be determined.

This slide also presents the search methodology used to obtain the dataset of Visian Implantable Collamer Lens reports in this presentation. Of note, the dates span from the approval of the MICL in December 2005 through May 1st, 2013. The MDR search found a total of 3,225 reports associated with the Visian Implantable Collamer Lens. A full description of the MDR search methodology and results are included with Appendix 2 in the FDA Executive Summary.

FDA conducted a systematic literature review through which 455 citations were identified. We note that the published literature may be reporting on U.S. or outside U.S. use of the device. And, furthermore, outside U.S. use could include other ICL models and sizing methods than those approved in the U.S. A full description of the literature review methodology and the results are included with Appendix 3 in the FDA Executive Summary. The applicant also provided a literature review to FDA.

Now I will discuss the pivotal trial conducted to support the TICL PMA. I will reference clinical data from the aforementioned sources as relevant to my discussion of the TICL study results. The applicant conducted a prospective, multicenter, non-randomized, and unmasked clinical investigation using the preoperative status of the treated eye as a control. Bilateral implantation of the investigational device was permitted. Duration of subject follow-up was one year.

The calculator was used to provide the physician with a recommended cylinder power and a range of sphere powers. The study calculator also provided a recommended ICL diameter. There was no control lens in this study.

The applicant expected to use MICL safety data to support safety of the toric modification. However, the MICL was not approved at the time that the TICL study was initiated. Therefore, this was an assumption made in the TICL study design.

A few safety parameters were listed in the study protocol, as shown on the slide. In addition, the protocol specified a suggested safety target based upon loss of best spectacle-corrected visual acuity. Effectiveness outcomes will be discussed in the subsequent presentation by Dr. Gene Hilmantel.

The TICL study protocol was approved over a decade ago. Therefore, it is important for us to note the differences between the TICL

study design and the study design that we would expect of such an investigation today.

One important safety consideration is visual disturbances. This topic is addressed in a toric IOL standard that has been published and is awaiting FDA recognition. That is ANSI Z80.30. Please note this TICL study was conducted between 2002 and 2007. ANSI began work on the toric IOL standard in 2000, but it was not finalized and published until 2010. While FDA found the Visian TICL study sufficient to grant approval on January 3rd, 2002, this comparison illustrates an evolution in thinking with regard to important elements of a phakic toric IOL study and is discussed in greater detail in the FDA Executive Summary. Most importantly, as outlined on this slide, ANSI recommends use of a validated questionnaire to assess visual disturbances, including assessment of spatial distortion related to axis misalignment. While the TICL study incorporated a questionnaire, it was not validated, nor did it include specific questions related to spatial distortion.

Since the study began in 2002, science and the development of patient-reported outcomes has evolved, prompting FDA to publish guidance for their development. This guidance was finalized in 2009 after the TICL study was completed. This guidance also stresses the importance of using a validated questionnaire.

The study cohort demographics are presented on this slide. 210 eyes from 124 subjects were enrolled. In the original application, the

applicant did not report protocol deviations. Gradually, over the many years which this file has been under review, FDA was notified of more and more deviations. The most recent count was provided by the applicant in the fall of 2013, listing 706 occurrences of protocol deviations, affecting 3,646 data points.

Subsequently, on December 20th, 2013, the applicant provided a table separating occurrences by severity. Please note that categorization by occurrence or data point was proposed by the Sponsor and may not be used with a consistent meaning. For example, some occurrences are equal to the number of eyes affected and others are equal to the number of data points affected. The words "major" and "minor" are also listed in quotes because these terms represent the applicant's recent assessment but are not necessarily consistent with actions taken.

For example, while three protocol deviations resulted in exclusion of study subjects, these deviations are listed as minor deviations under eyes outside of the inclusion criteria. Furthermore, unapproved randomization is listed as a minor deviation. However, this reflects use of an unapproved protocol at a study site that resulted in an integrity hold, as described in the regulatory history presentation.

Split between minor and major deviations, 143 of the 210 implanted eyes, or 68%, were implanted with lenses not according to protocol. That is, either sphere or cylinder power was outside of specified

ranges, axis was outside of the protocol-specified four axes, or lens diameter was not selected by the approved method. We note that when the lens length was not selected according to the protocol, these deviations might have affected safety outcomes by avoiding adverse events, which will be discussed later in my presentation. Overall, the protocol deviations included a large number related to out-of-window visits, missing data, failure to collect protocol-required data due to inadequate case report forms, including failure to verify one exclusion criterion, use of a non-FDA-approved protocol at one site, and implantation of TICL models with parameters not permitted in the study protocol.

Please note that there were 210 eyes in the study cohort. All 210 eyes were subject to at least one protocol deviation, and more than one deviation can occur in each eye.

Regarding the clinical impact of the deviations, the applicant has provided some sensitivity analyses. However, we note that the applicant has not addressed all outcomes. For example, the applicant has focused on the categories which they perceive as major deviations, but there are other categories of significant concern. For example, the applicant lists categories pertaining to missing data as minor deviations. However, due to the volume of missing data in the TICL study, FDA would generally classify this as a major deviation. Note that based on subcategorizations of missing data provided by the Sponsor, 93 eyes are missing some observed lens orientation data.

We do not know how many of these 93 eyes are also affected by the other subcategorizations of missing data. Therefore, the total number of eyes with missing data is estimated to be at least 93. In particular, we note that the volume of missing data makes it very difficult to analyze the effect of these deviations except through unverifiable assumptions.

One possible explanation for confusion regarding the approved parameters for the study lens involves an error in the power and diameter measurements of the ICLs. ISO 11979-1 defines the labeled IOL power as the power of the lens in situ. After enrollment for the TICL study was completed, FDA became aware from the data in the MICL PMA that each TICL had been labeled with the incorrect power and overall diameter. The use of saline rather than balanced salt solution to hydrate the lens increased the power of the TICL above the physiological value and underestimated the overall diameter in the eye. The applicant determined an average correction factor for the power and dimensions and has relabeled the spherical and cylindrical power as well as the dimensions of the TICLs used in the study.

We note that similar issues of conversion for measurements in 0.9% saline to those in BSS occurred in the myopia ICL investigational trial and became known to FDA after the Panel meeting in 2003.

FDA accepted the applicant's proposed corrective actions for the MICL, including modifications to labeling and the software used to select the appropriate lens diameter and power. These changes were made before

the MICL was approved and marketed.

This slide summarizes the differences between the lens parameters approved for the study, those actually studied, and those proposed for marketing. These parameters are listed in both saline and BSS hydration to allow a more convenient comparison. However, we note that the parameters approved in the study protocol were based on measurements taken in saline.

Note that the protocol was only approved to study spherical powers down to -21 diopters in saline hydration. However, spherical powers down to -23 diopters were actually studied. Similarly, cylinder powers down to 1.5 diopters in saline hydration were approved in the study. However, cylinder powers down to 1 diopter were actually studied.

Finally, please note that the study was approved to study four axes of cylinder correction, 0, 45, 90, and 135 degrees. TICLs were intended to be rotated up to 22.5 degrees to the correct axis alignment for each subject. In contrast, the study implanted 80 axes ranging from 3 to 179 degrees. This occurred because manufacturing of the TICLs was altered from what had been approved by FDA to include some customization of the cylinder correction axis within a certain range. In addition, the TICLs were labeled with the exact cylindrical axis generated, which led to the potential for axes to range from 1 to 180 degrees.

Finally, the ICL currently proposed for approval has

specifications measured in BSS. The proposed toric power calculator to be used with the BSS hydrated TICL has been modified from the study calculator to output the appropriate powers and diameters based on the BSS hydration. Note that the numerical value for the powers proposed are even numbers in BSS whereas the actual studied powers were uneven numbers in BSS based on the conversation factor calculations. The exact powers proposed for approval have not been studied.

271 ID numbers were assigned in the clinical database, 21 numbers were not assigned to an eye but used to test the database, and 19 subjects did not receive an implant. Therefore, of the 231 eyes that received implants, some were MICLs placed in the fellow eyes of toric subjects. Others were placed outside enrollment criteria. Therefore, there were 210 eyes from 124 subjects in the TICL study cohort. 124 were primary eyes, and 86 were fellow eyes. In three of these eyes, the TICL was ultimately explanted, and these eyes were discontinued from the study.

The FDA-recognized ISO intraocular lens standard 11979-7 states: "To minimize the uncertainty in the data, the loss to follow up in one-year investigations should be less than 10%." In the TICL study, 69.5%, that is 146 of 210 eyes were available for analysis within window at the 12-month postop visit. After taking into consideration the number of discontinued eyes, this leads to an accountability of 70.5%, or 146 of 207 eyes. Using all visit data, including out-of-window visits, accountability rises to 93.7%.

The Panel will be asked to discuss the following question: In light of the study conduct, including but not limited to the 3,646 data points affected by protocol deviations; a significant amount of missing data; within-window accountability of 70.5% at 12 months; and 68%, that is, 143 of 210 eyes implanted with lenses not according to protocol, do the data generated from the TICL study represent valid scientific evidence for assessment of device safety and effectiveness?

Now we will discuss the available safety data for the TICL lens platform. Please be reminded that the ICL sits behind the iris and in front of the natural crystalline lens. Inappropriate vaulting of the ICL in this tight space can result in adverse events. For example, excessive vault could lead to narrowing of the anterior chamber angle or rubbing of the ICL on the iris. Insufficient vault may damage the natural crystalline lens, potentially causing cataract.

The applicant met the protocol target specified for the maintenance of best spectacle-corrected visual acuity. The table above lists cumulative adverse events seen in all eyes of the TICL study. The applicant has noted that the only rates exceeding the safety and performance endpoints specified in the ISO standard are those for retinal detachment and surgical reintervention. Persistent adverse event rates were also comparable to ISO's SPE in both the FDA and the applicant's Executive Summary and are not listed on this slide.

In addition to the adverse events listed on the previous slide, surgical or perisurgical complications occurred in 12 eyes in the TICL study cohort. One case was observed at one day postoperatively to have excessive forward vault of the ICL of approximately 200% of the corneal thickness with a normal IOP. At four months postoperatively, the vault was observed to be within a normal range. The applicant has stated the possible-retained viscoelastic material might have caused the transient increase in vault. We will discuss ICL vault in greater detail after summarizing overall adverse events since many adverse events can be linked to inappropriate vaulting of the ICL.

In comparison with the overview of adverse events from the TICL study, we will now discuss similar data from other sources. As described earlier, the MICL post-approval study followed the same study cohort enrolled in the MICL pivotal trial for a longer duration of time. In some cases, this was greater than five years. Some key safety results are shown here to compare to the data seen in the TICL trial. Please note that these Kaplan-Meier percentages are estimated risks to an individual eye or patient based upon the declining number of patients that are available over time. These are more realistic estimated risks that simply using the number implanted as the denominator.

Another source documenting adverse events is our MDR database, which I described earlier. 3,225 MDR reports between

December 22nd, 2005 and May 1st, 2013 were reviewed for our analysis. The findings were grouped into a few categories of interest. Please remember that terminologies are not consistently used in the MDRs, and multiple terminologies may be reported in the same report. This table shows the findings from the review of the MDRs, including 1,590 reports, or 49.3% related to vaulting, such as excessive vaulting, low vaulting, and inadequate vaulting. 1,566 MDRs described that that lenses were removed or explanted. 1,336 MDRs reported that the lenses were replaced or exchanged.

Now we will take a closer look at a few specific findings. Anterior subcapsular opacities, or ASOs, were observed postoperatively in six eyes, or 2.9%, in the TICL study. Two of these cases were classified as clinically significant. In another case, one TICL was explanted at one-week postoperatively for ASO, though asymptomatic. Thus, although an opacity may not meet criteria for clinical significance, development of a lens opacity could potentially lead to a secondary surgical intervention, which is a clinically significant adverse event.

During the pivotal trial for the MICL PMA, anterior subcapsular opacities and nuclear cataracts were observed, some of which were clinically significant. Of note, some opacities were observed in the first postoperative week.

As described earlier, the MICL post-approval study followed the same study cohort for a longer duration of time, in some cases, greater than

five years. Complications seen at a rate greater than 2% include: anterior subcapsular opacity in 31 eyes, or 5.9% -- however, we note that not all were clinically significant; abnormal pigment in the angle was noted in 4.89% of eyes; pigment deposition on the IOL was noted in 8.37%; and transillumination defect was noted in 9.89%.

The per-person rate of new clinically significant anterior subcapsular opacity was slowly but consistently increasing over time, .33% incidence of new cases per year over the entire seven years of follow-up. Reduction of hazard of approximately 30% was seen with each diopter of decrease in negative lens power.

In our MDR analyses, we noted 298 MDRs related to cataract. In our literature review, 18 cohort studies were identified with findings in cataract formation. Incidence of anterior subcapsular cataract formation in Visian phakic IOL ranges from 0 to 28% in the literature, with average follow-up of 39 months, ranging from 6 to 120 months.

Now we will discuss secondary surgical interventions. In the TICL study, SSIs were reported in six eyes. In addition to one retinal detachment repair, there were five Visian TICL-related surgeries. Three eyes were discontinued from the study in which the TICL was removed with no subsequent IOL or ICL implantation. One of these was due to excessive vault, one due to asymptomatic anterior subcapsular cataract, and one related to a visual disturbance.

One TICL was replaced because the lens was too long, causing iridocorneal touch secondary to excessive vault. One TICL was repositioned three days after the surgery. The TICL had rotated approximately 25 degrees counterclockwise from the desired position.

In the MICL pivotal trial, the reported incidence of secondary surgical reinterventions was 3.1%, as reported in the summary of safety and effectiveness data at the time of approval. In three eyes, the MICL was removed. In four eyes, the MICL was repositioned. In eight eyes, the MICL was replaced. And in one eye, the MICL was replaced, then removed. As can be seen from these events, vault was identified as a significant safety concern at the time of the MICL approval. We evaluated all MDRs related to explantation and attempted to identify the cause. As shown in this table, inappropriate vault accounts for the vast majority of ICL explantations reported to FDA.

When recorded, vault in the TICL study ranged between 0% and 400% of corneal thickness. There was significant within eye variation, from 0% to 225% of corneal thickness. The applicant has suggested that, optimally, vault should be between 50% and 150% of corneal thickness. Forty-eight eyes had maximum vault greater than 150%, while 44 eyes had minimum vault less than 50% at some visit. Thus, 44%, that is 92 of 210 eyes, had a vault outside of the optimal range at some visit. The observed vault data was variable for many eyes over the course of the study. It appears that

either this measurement technique has significant imprecision in the hands of some investigators or that the lens vault can change considerably within several months.

Please note that the proposed labeling states the following regarding postoperative Visian TICL vaults, and similar information also appears in the approved myopia ICL labeling: Lens vault, that is, the distance between the anterior surface of the crystalline lens and the posterior surface of the Visian Toric ICL, should be assessed 24 hours postoperatively at a slit lamp. Although the postoperative vault of the Toric ICL is intended to be approximately equal to the central corneal thickness, we believe that the optimal vault should be between 50% and 150% of central corneal thickness, this being equivalent to a range of 250 to 900 microns. However, in the absence of symptoms, lens vault outside of this range may not necessarily require exchange or removal.

Please note that the proposed labeling states the following regarding postoperative Visian TICL removal: "It is recommended that the Visian TICL be removed in cases where the vault is insufficient and the patient exhibits early anterior subcapsular cataract. Removal of the Visian TICL may be necessary in cases where the vault is excessive, causing narrowing of the anterior chamber angle, thus decreasing aqueous flow. Visian TICL removal may also be necessary for other reasons on an individual basis. The risks involved in Visian TICL replacement have not been studied and are unknown."

The picture on this slide was provided by the applicant as an example of training materials used. It is unclear how the applicant concluded that the range 250 to 900 microns is the optimal amount of lens vault. We note the following: The method described using corneal thickness as a reference is inherently difficult to perform at the slit lamp, may lack objectivity, and central thickness of normal corneas can vary within a wide range of values, from 450 to 650 microns. An alternative would be to make an objective assessment of vault measurements using imaging tools, such as ultrasound biomicroscopy, optical coherence tomography, or Scheimpflug photography. However, this would still require some recommendations as to what constitutes unsafe vaulting, as determined by objective methods.

The Panel will be asked to discuss the following question: Does the labeling provide adequate instruction with regard -- regarding evaluation of postoperative lens vault?

Concern regarding excessive and poor vault was raised during approval of the MICL within published literature through MAUDE database reports and also within the TICL study. The published literature raises concern regarding the predictability of postoperative vaulting. Please note that many variable and sometimes unmeasurable factors have been identified in the literature as potentially impacting ICL vault, including positioning of ICL footplates or haptics in relation to the sulcus and ciliary body, orientation of ICL plate haptic major meridian, degree of myopia,

accommodation, age, lighting, and time from lens implantation. Finally, the manufacturing of the TICL results in variability of the Sagitta value, that is, distance from the plane of the footplate to the corner of the posterior optic surface, which along with the power of the posterior surface of the TICL will affect clearance of the TICL.

Based on the applicant's communications to FDA, there appears to have been an evolution in thinking regarding the appropriate position of the TICL over the past decade. In the approved TICL study protocol, the applicant stated that the ICL footplates fit snugly in the sulcus. In the TICL PMA, the applicant specified this position within the proposed IFU language for the TICL. "The Visian TICL is intended for placement in the posterior chamber ciliary sulcus of the phakic eye."

However, the applicant recently communicated to FDA that the footplates at the four corners of the lens are designed to interact with the ridges and grooves on the surface of the ciliary process, and in the majority of cases, the ends of the footplates remain on the ciliary processes. However, in instances where the ends of the footplates come into contact with the sulcus, compression forces may be created. This results in a change in the curvature of the haptic and may increase lens vault. We note that the snug positioning in the sulcus originally described is now felt to potentially lead to increased lens vault. Furthermore, it is not clear whether surgeons can be expected to reliably and consistently achieve the type of positioning now

described by the applicant, in which the ICL footplates are expected to sit upon the anterior portion of the ciliary body.

It is well known that ICL size relative to sulcus-to-sulcus diameter affects ICL vault. Very small changes in the compression of the TICL result in large changes in the vault relative to the clearances in the eye. Just 0.3 mm of compression can cause a change in ICL vault of approximately 550 microns. As mentioned previously, the applicant recommends that an optimal clearance or vault over the crystalline lens is 250 to 900 microns. Thus, if the footplates are sitting in the ciliary sulcus, a slight mismatch in size can cause significant changes in vault. Sizing in this clinical study was generally based on white-to-white, which is poorly correlated with sulcus-to-sulcus diameter.

In the literature, some users have used other sizing methods and reported on them. In both cases, subjects were reported to have had poor outcomes potentially due to poor sizing, i.e., excessive vault and poor vault.

During the study, although investigators were expected to use a sizing method based on white-to-white diameter and anterior chamber depth, some investigators used UBM or other sizing methods. In some cases, the reasoning given for use of the alternate methods was that investigators were trying to avoid inappropriate vault based on fellow eye data or personal preference.

The TICL proposed labeling makes sizing recommendations based on white-to-white diameter and anterior chamber depth, although the potential use of alternate methods is alluded to without specific instruction. Furthermore, it is unclear what sizing method is used in the postmarket for the MICL, as cited in the literature. While approved labeling may advise selection of one size, other sizing methods are reported to be used.

The Panel will be asked to discuss the following question: Based on all available data and the sizing method used in the clinical studies, do you believe that the directions for use concerning sizing are adequate to reasonably ensure predictable and safe postoperative vaulting?

No endothelial cell loss data was collected as part of the Visian TICL study, with the assumption that the safety data from the approved MICL, that is, from the pivotal trial and post-approval studies, would address this safety issue. The pre-approval data for the MICL showed an acute post-surgical endothelial cell density loss of about 3% and indicated a continual study loss of 2.2% per year.

To put this number in perspective, mean endothelial cell loss per year in normal adults had been reported to range from .22 to .6% in published literature. Contraindications in MICL labeling provided minimum ECD criteria as functions of age that should result in at least 1,000 cells/mm^2 at 75 years of age. In the post-approval phase, specular microscopy showed a cumulative loss of 11% over the 5+ years. However, looking only at the

mean loss masks some more significant losses which occurred in a subset of subjects.

For example, 10 eyes had significant endothelial cell loss, that is, greater than 30% loss from baseline, at five years postoperative or greater that did not seem directly related to surgical trauma, but rather to long-term endothelial cell loss. These represent approximately 6% of the 159 eyes with endothelial density counts at 5+ years postoperatively, and 8.7% of the 115 with both preoperative endothelial cell density and endothelial cell density data at 5+ years postoperatively. However, there was no control group, and the result may not be representative of the initial cohort because there was greater than a 20% lost-to-follow-up rate as well as over 30% missed visit rate. We note that these 10 eyes were not designated as outliers by any standard statistically methodology. They simply represent part of the cohort and had poor outcomes.

The applicant has presented data from long-term follow-up of these 10 eyes. We would like to note the following regarding the extended follow-up. Prior to the 10-year postoperative visit and subsequent to the 5-year visit of the post-approval study, 3 of these 10 eyes had undergone cataract surgery, which included removal of the Visian ICL and implantation of an aphakic IOL.

One MDR reported an ICL explanted due to endothelial cell loss. As you can see from the numbers on the slide, endothelial cell count in

this subject decreased 67.7% between an exam in 2009 and an exam in 2010.

We also note that 30 MDRs in our analysis were related to corneal edema or decompensation. However, based on the limitations of MDR reporting that I previously discussed, it is very difficult to distinguish in every case if these events were related to long-term endothelial cell loss versus surgical trauma. Many but not all of these events were observed in the immediate postoperative period.

In our literature review, mean endothelial cell loss ranges from 2 to 12%, with an average follow-up of 30 months, ranging from 12 to 48 months. We note that limitations on literature data include the following: The population receiving this lens includes high myopes, and typical endothelial cell loss in high myopes is not well documented. Also, few papers on endothelial cell loss report on the proportion of eyes that lose a larger number of cells. Most just report mean losses. Issues surrounding endothelial cell loss will be discussed further by Dr. Youlin Qi in the presentation in the proposed post-approval study for the TICL.

Long-term data regarding endothelial cell loss in the literature often has limitations. We note that the data presented by the applicant to demonstrate ECL after cataract surgery had many limitations, as identified by Dr. Alan Sugar at the time the article was published. First, the data was from cataract extractions performed from 1976 to 1982. Next, the techniques used, including cryoextraction, are not consistent with modern cataract

surgery. Finally, there was potential selection bias and significant loss to follow-up in the study. Of the 57 patients with data at 10 years, only 7 had posterior chamber IOLs. Finally, Dr. Sugar notes that the current cell loss would be expected to be very different with the use of phacoemulsification and viscoelastics.

The Panel will be asked to discuss the following question: Potential adverse events identified in the available clinical data pertaining to the TICL lens platform include inappropriate vault, cataract formation, secondary surgical interventions, endothelial cell loss, glaucoma and narrowing of the angle. Given the available treatment alternatives for lower myopes, do you believe the safety profile of the TICL warrants approval of the full range of spherical equivalent powers proposed for approval, that is, -3 diopters to -16 diopters?

Now Dr. Gene Hilmantel will present on the effectiveness data for the TICL study.

DR. HILMANTEL: Good morning. My name is Gene Hilmantel. I'm a clinical reviewer for the Division of Ophthalmic and ENT Devices. I will be discussing the effectiveness aspect of this submission.

First, I'm going to provide a little bit of general background about toric IOL effectiveness. There are three factors that are of greatest importance in determining how effective a toric lens is. The main device-related factor is the accuracy of the axis alignment. There is about a 3.3%

reduction in astigmatism correction for each degree of misalignment. Obviously, this can be affected by surgeon skill and surgeon error. The second and third factors determine whether the best IOL cylinder power is selected and whether the target for the axis orientation is correct. For IOLs used in cataract surgery, the critical measurement is the preoperative corneal cylinder, but for a phakic lens is measurement of the refractive cylinder.

The incision can induce a change in the corneal shape, thereby altering the eye's cylinder power and axis. If this is not correctly predicted, there is a loss of effectiveness. These last two factors, in most cases, are usually small effects, but for low cylinder corrections on the order of 1½ diopters or less, the errors in predicting the incisional effect or in measurement can cause large percentage changes in cylinder reduction.

If the device makes correct axis alignment easy to achieve and stable, the effects are reduction in manifest astigmatism, which then causes improved uncorrected visual acuity, which in turn can lead to patient satisfaction. The latter three are a result of the device being effective as well as good surgical skill. As mentioned previously, the manifest astigmatism may also be affected by inaccurate measurements and by the incisional effect, as well as by refraction technique and patient subjective responses. Uncorrected visual acuity is affected more by spherical refractive error than by cylindrical error, and patient satisfaction is affected by many psychological factors.

Accurate axis alignment can be influenced by difficulties in achieving the correct orientation intraoperatively and surgeon error, and by rotation of the lens postoperatively. For toric IOLs that are placed in the bag, capsular fibrosis may help fixate the haptics. For the ICL, which sits between the iris and the crystalline lens, there is no fibrosis to fixate the haptics. This raises theoretical concerns regarding postoperative rotational stability. In recent communications, the applicant states that the ICL footplates usually sit on the anterior portion of the ciliary body and that the footplates interact with the ridges and grooves on the surface of the ciliary processes, thereby providing frictional stability.

The protocol for the STAAR ICL clinical study listed six effectiveness parameters. Three of these pertained to the manifest refraction results. The decreases in refractive cylinder and myopia designated the primary efficacy variable; the predictability or accuracy of the refractive changes compared to the intended correction; and the refractive stability, in other words, the changes in manifest sphere and cylindrical outcomes over time.

One of the effectiveness parameters in the protocol was improvement in uncorrected visual acuity, one was patient satisfaction, and one was rotation of the ICL. These parameters all correspond to factors in our earlier discussion of general toric lens considerations. The targets listed in these two slides under the predictability of refractive outcomes and

improvement in uncorrected acuity were referred to in the protocol under the heading of endpoints.

STAAR's Toric ICL clinical study protocol was created and approved a decade ago. Since that time, the thinking of the ophthalmic community concerning appropriate study design has evolved. After the protocol was approved, an ANSI committee started work on a standard which would outline important elements for an appropriate study design.

In 2010, ANSI published Z80.30, a standard for toric IOLs. It included recommendations for toric modifications of both aphakic and phakic IOLs. The recommended main effectiveness outcomes were percent reduction of manifest cylinder -- that means achieved reduction over attempted reduction -- and lens axis misalignment. Rotational stability was also to be assessed, ANSI's criterion that the stability is established if 90 percent of the eyes rotate less than 5 degrees between adjacent visits at least three months apart.

The ANSI standard states that the method used to measure axial misalignment should have sufficient precision to detect a 5-degree change in rotation. It references an image capture method with appropriate precision. It also states that the method should adjust for head tilt, for example, by utilizing registration to details of the iris.

Now I'll discuss the study effectiveness outcomes. For the 194 eyes with both preoperative and 12-month or later refractions, the mean

postoperative manifest refractive cylinder was 1.95 diopters. The mean 12-month cylinder was 0.52 diopters. The mean change from baseline was highly significant. The mean manifest refraction spherical equivalent went from -9.38 diopters at baseline to +.03 diopters at the end of the study.

Here, we provide the percent reduction of cylinder stratified by the preoperative cylinder. The percent reduction of cylinder is calculated for each eye by dividing the achieved reduction by the attempted reduction. These figures provide the average percent reduction for all 194 eyes with a visit at 12 months or later.

Note that the reduction in cylinder can be calculated either in the spectacle plane or in the corneal plane. While the calculation in the spectacle plane is more natural, being taken directly from the phoropter results, spectacle plane changes are affected by the level of baseline myopia. Eyes with high baseline myopia will show greater changes simply due to the reduction of the myopia from the implant. Even a spherical ICL implant will cause a reduction in cylinder as measured in the spectacle plane.

Corneal plane calculations are not affected by the correction of myopia related to the implant. In this table, the rows represent the stratifications, the different levels of preoperative cylinder. The first row shows results for all eyes combined. The first column shows the level of preoperative refractive cylinder. The third column shows the mean percent reduction in the spectacle plane, while the fourth column shows this

reduction calculated in the corneal plane. For percent reduction of cylinder, the worst-case results are generally those for the lowest level of cylindrical correction. For eyes with 1 diopter of preoperative manifest cylinder, the mean percent reduction was 75% in the spectacle plane and 66% in the corneal plane. For these eyes, the mean dioptric reduction was 0.64 diopters in the spectacle plane.

The question arises as to how the surgically induced astigmatism may have affected the results for the decrease in refractive cylinder. The protocol instructed investigators to always use a temporal incision no more than 4 mm in length. As noted earlier, STAAR uses software they call their toric calculator to help the surgeon select the appropriate Toric ICL powers. This toric calculator assumes that the incision has no effect upon the corneal astigmatism.

The applicant analyzed the corneal surgically induced astigmatism created by the incision. The analysis included 189 eyes with 12-month keratometry data. The average magnitude of the surgically induced astigmatism was 0.66 diopters. In looking at the distribution of the individual vector changes in the corneal astigmatism, STAAR reported that the spatial median was 0.2 diopters of induced with-the-rule astigmatism.

To try to assess whether these corneal changes may have accounted for a portion of the observed reduction in cylinder, FDA requested an additional analysis. We asked the applicant to vectorially add the change

in keratometry to the preoperative manifest cylinder for each eye to simulate the outcome from implantation of a non-toric ICL. This simulation indicated that for most ICL cylinder powers, the surgically induced astigmatism would likely have caused mean increases in refractive cylinder rather than decreases. For only the 3.6 diopter cylinder power lens, the simulation indicated that there would likely have been a decrease in refractive cylinder of about 0.4 diopters.

The predictability is just another word for accuracy of the refractive correction. This compares the achieved change to the attempted change for each eye. It is calculated for refractive cylinder and for manifest refraction spherical equivalent. For refractive cylinder, 92% of eyes were within 1 diopter of the intended refraction, and 70% of eyes were within ½ diopter of the target. For MRSE, 97% were within 1 diopter of the attempted correction, and 77% were within ½ diopter. All of these results exceeded the protocol-defined targets for these outcomes.

Here, we're looking at an analysis of the stability of the manifest cylinder based upon changed in the magnitude. This analysis looks at the changes within individual eyes across pairs of adjacent visits. As shown in the columns, the paired visits reported here are 1 to 3 months, 3 to 6 months, and 6 to 12 months.

The first row with data shows the percent of eyes that changed less than or equal to 1 diopter between the postop visits while the second

row shows the percent that changed less than or equal to ½ diopter. In all cases, at least 98% of eyes changed less than or equal to 1 diopter between the visits shown. The third row with data shows the mean diopter changes between visits. On average, postoperative refractive cylinder magnitude did not substantively increase or decrease over the time spans shown.

This table gives similar data concerning refractive cylinder vector changes between pairs of adjacent visits. Vector changes incorporate shifts in axis as well as magnitude. Also note that vector changes are always positive in magnitude. The mean changes in vector magnitude shown in the third row of data include changes related to the imprecision of the refractive measurement. All the mean changes in vector magnitude were about ¼ diopter. For reference, I note that, for the lowest Toric ICL cylinder power used in the study, a 30-degree axis shift would cause a vector change of about .6 diopters in magnitude.

No eyes had uncorrected acuity of 20/40 or better at the preoperative visit. At 12 months or greater, postoperatively, 95% of eyes were 20/40 or better. There were 159 eyes present at 12 months or greater that had preoperative best-corrected acuity of at least 20/20. Of these, 100% achieved 20/40 or better. The protocol target was exceeded. Note that uncorrected acuity is affected much more by changes in spherical equivalent than by cylinder.

Patient satisfaction was assessed using a non-validated

questionnaire. For each eye, patients were given a questionnaire asking, were you satisfied with the surgery? Patients were asked to categorize their satisfaction as extremely, very, fairly, moderately, or unsatisfied. There were 188 forms filled out at 12 months or greater; 98%, 180 out of 184, contained responses of extremely or very satisfied.

In this slide, I have posted the percents based upon the total number of non-discontinued eyes, 207. 11% of the 207 did not have a response either due to a protocol violation of not being given the questionnaire or due to the subject missing the visit.

Subjects were also asked, would you have ICL surgery again? 98% of the 184 available eye forms said yes. Again, 11% of the 207 were missing responses.

As pointed out earlier, rotational misalignment measured at the slit lamp is the most direct measure of device effectiveness. Relying upon vector changes in manifest cylinder is problematic for the lower Toric ICL cylinder powers. The lowest two ICL cylinder powers in the study were .8 diopter and 1.2 diopters. These correspond to approximately 0.6 diopters and 0.9 diopters in the corneal plane. Between these two powers, there were 67 implants, about a third of the total. Rotations of 15 degrees for these lenses would cause a change in refractive cylinder magnitude of less than ½ diopter.

This figure shows the diamond-shaped alignment markings that

determine the long axis of the Toric ICL. The long axis is the longer dimension of the plate haptic, in this picture, the horizontal line. It should not be confused with the cylinder axis that was manufactured into the optic of the lens at 0 to 180 degrees from this long axis meridian. Note that the lens is delivered with customized instructions telling a surgeon how much to rotate the long axis from the horizontal in order to orient the cylinder axis in the appropriate position.

The applicant stated that the investigators were asked to examine the patient at the slit lamp and estimate the orientation of the long axis of the Visian TICL based upon the alignment markings or haptic edges if visible. Please note that the orientation markings in the lower right and upper left corners have nothing to do with cylinder. They are there to guide the surgeon in implanting the lens right-side up.

This figure is taken from the postoperative case report forms. The investigator was instructed to circle the observed orientation of the long axis of the Toric ICL corresponding to the closest 15 minutes in clock hour position or to write in a clock hour position. In some cases, the investigator wrote in the orientation of the axis in degrees, and in other cases, the investigator wrote the number of degrees shift from the horizontal.

The applicant reported that there was no standard operating procedure for investigators to make this assessment. For example, there was no required use of reticle with angle markings. Investigators were not

specifically instructed to avoid looking at the intended orientation or at prior observations when making this measurement.

In the original Toric ICL submission, the applicant provided an analysis of 13 eyes with greater than 15 degrees Toric ICL rotation between visits. Based upon inconsistencies with refractive cylinder data, the applicant stated that it appeared that there were significant errors in some of the rotational misalignment measurements. FDA requested clarification in the first major deficiency letter. In their response, the applicant stated that they audited eyes with significant rotation or misalignment. They modified several analyses and some data. In this submission, they also acknowledge that the clock hours methodology was clearly a very gross approximation and subject to considerable opportunity for error.

Due to the fact that this response provided some analyses and data that contradicted those in the earlier submission, FDA requested further clarification in the second major deficiency letter. In the letter, FDA stated that it appeared possible that the observations of axis orientation were unreliable and that these analyses my not provide useful information. Furthermore, "Your analyses of refractive error of angle may provide more reliable information concerning ICL axis changes." FDA asked that the applicant provide a discussion of reasons for the difference between the original observations and the analyses in the revised version, but stated that, alternatively, "You may retain the original data and analyses and rely

primarily upon the refractive data for information concerning axis position if the direct axis measurement method was too gross to be very useful." The applicant agreed to the latter alternative.

In the interest of completeness, we're presenting rotational misalignment analyses based upon the two methods used, the direct measurement method and the error of angle method. The error of angle is defined as the angular difference between the achieved treatment and the intended treatment calculated from manifest cylinder through vector analysis.

We note that after the independent audit of the data requested by the FDA Office of Compliance, some of the direct measurement data changed significantly. In some cases, these changes eliminated some of the apparent errors in the earlier submissions.

Here, we have the key results for the direct measurement of the rotational misalignment. The three rightmost columns characterize the distribution of the axial misalignment of eyes in the study population at 3 months, 6 months, and 12 months or greater. The rows of data represent the percentage of eyes that have misalignments from the intended position of less than 10 degrees, 20 degrees, or 30 degrees.

So at the 12-month visit, 87% of eyes were misaligned less than 10 degrees, 96% less than 20 degrees, and 99%, all but two eyes, were misaligned less than 30 degrees. Note that nine eyes were intraoperatively

placed at greater than or equal to 15 degrees from the intended position. Also note that two eyes had early secondary surgical interventions that greatly reduced large surgical or Day 1 misalignments. The figures in the table reflect the post-intervention observations for these two eyes.

The applicant analyzed the lens rotation between adjacent visits. At least 94% of eyes had less than or equal to 5 degrees of rotation between the pairs of visits shown here. The rotational misalignment analyses also included a significant number of eyes seen outside the protocol-defined visit windows. These created inconsistent time spans between visits, making stability analyses somewhat problematic. We note that this issue is relevant to all methods of analyzing postoperative stability.

There was a significant amount of missing data for the rotational misalignment parameter. 22% of the 1249 potential postoperative rotational misalignment observations were missing either due to protocol violations or missing visits. 39% of potential Day 1 observations were missing, as were 30% of 6-month observations, and 11% of 12-month observations.

Here, we have the key results for the vector error of angle analysis of rotational misalignment. At 12 months or greater, 70% of eyes had rotational misalignment less than 10 degrees. 90% had misalignment less than 20 degrees. And 97% had misalignment less than 30 degrees, with six eyes showing misalignment greater than 30 degrees.

By this vector analysis method, at least 75% of eyes showed less than or equal to 5 degrees of axial rotation between the adjacent visits shown. This analysis seems to indicate that after six months postoperatively, there are still 16 eyes rotating more than 15 degrees between visits and five eyes rotating greater than 30 degrees. However, this error of angle result should be interpreted with caution.

The vector error of angle method has significant limitations. There was no standard operating procedure for performing manifest refraction. When there are low levels of residual manifest cylinder, there is substantial imprecision in the measurement. Perhaps of greatest importance, for low Toric ICL cylinder corrections, the error of angle method can easily have high numbers of false negatives and false positives in detecting axial rotation. 47% of eyes were implanted with fairly low cylinder power. For example, the lowest cylinder power used in the study corrects only about .6 diopters in the corneal plane, and even 15 degrees of misalignment would likely fall within measurement error.

The Panel will be asked the following question: Rotational misalignment and axial stability were assessed by direct observation and manifest refraction. In light of the following:

- Limitations of each method;
- Missing data, 22% of all postop direct measurements; and

- Out-of-window visits at 123 instances

Do the rotational misalignment and manifest refraction data provide reasonable assurance that the Toric ICL can achieve desired axial orientation and rotational stability?

The Myopia ICL was implanted with the long edges of the haptic in a horizontal orientation. The Toric ICL must, at times, be surgically rotated intraoperatively from the horizontal in order to place the cylinder axis in the correct orientation. The absolute value of this angle of rotation from the horizontal is defined as the fixation angle. Fixation angle can be from 0 degrees horizontal placement to a maximum of 22½ degrees. In most eyes, the ciliary sulcus is not round but has a vertical oval shape.

In a paper published in 2012, Mori raised a theoretical concern that surgical rotation might cause some of the footplates to become loose, as shown in the diagram by the red arrow. This could conceivably cause eyes with larger fixation angles to be less stable than eyes with small fixation angles.

Mori studied this issue in a sample of 58 eyes implanted with Toric ICLs followed for six months postoperatively. He found a small but significant correlation between the intraoperative fixation angle and the postoperative Toric ICL rotation. Eyes with fixation angles greater than 5 degrees were 5.6 times as likely to have postop rotation as eyes with smaller fixation angles.

The results from the IDE study demonstrated only a weak relationship between fixation angle and postop misalignment at 12 months. In this table, each row represents a different fixation angle bin. The leftmost column gives the fixation angle while the two rightmost columns provide the mean postop rotational misalignment, as measured by the two methods previously discussed, the error of angle calculated from the manifest and the misalignment from direct slit lamp measurement. Note that the bottom row contains only a single case. It was related to a protocol deviation in which there was an intraoperative rotation of 90 degrees resulting from the shipment of a lens with incorrect lens axis.

Eyes with fixation angle of 16 to 22 degrees appeared to have the largest postop rotation. One of the analyses found a statistically significant correlation between the fixation angle and 12-month misalignment, p=.02, r=.16, but other analyses found non-significant results.

The Panel will be asked the following question: Fixation angle is the amount of intraoperative surgical rotation used to achieve the desired TICL axial orientation. 17% of eyes in the Visian TICL study had a fixation angle greater than 15 degrees. Some published literature indicates that large fixation angles may be associated with greater postoperative rotation. Is there sufficient information available to support directions for use with fixations up to 22½ degrees, as in the proposed labeling?

Now Dr. Youlin Qi will present the post-approval study

considerations.

DR. QI: Good morning, my name is Youlin Qi. I'm the epidemiologist from Division of Epidemiology in the Office of Surveillance and Biometrics.

Before we talk about post-approval studies, we need to clarify a few things. The discussion of a post-approval study prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting the device is safe and effective. The plan to conduct a post-approval study does not decrease the threshold of evidence required by FDA for device approval. The premarket data submitted to the Agency and discussed today must stand on their own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate benefit/risk balance.

Through review of the premarket data, the FDA review team has identified postmarket concerns that may need to be addressed if this first-of-a-kind device is approved. This includes: progressive endothelial cell density loss, as it is not clear what device performance will be in terms of the mean ECD loss and the proportion of eyes with large ECD loss; the possibility of late cataract development and its association with vault change -- long-term cataract development is a concern for this device because of closeness to the natural lens, which can result in vault change; the stability of the corrected cylinder axis over time -- because of the toric feature of the device,

maintaining the cylinder axis stability is essential to the visual acuity and patient satisfaction; and visual disturbances after TICL implantation evaluated by patient questionnaire, as recommended by the FDA's guidance for patient-reported outcomes.

FDA received a revised post-approval study proposal through impacted review on January 8, 2014, which was sent to the Panel members as an addendum in the second Panel mail-out. The study design is a single-arm, prospective, multicenter clinical study. A total of 150 patients with up to 300 treated eyes will be enrolled from 5 to 10 clinical centers in the United States.

The study endpoints are printed along with the corresponding proposed sample size and the follow-up schedule. First, endothelial cell counts in a minimum of 100 eyes at the study completion who are followed for five years. The hypothesis test will be conducted at end of five years with a targeted maximum mean loss of 18%.

Second, instance of clinically significant anterior subcapsular cataract development, with a minimum of 100 eyes at study completion who are followed for five years. The hypothesis test will be conducted at the end of five years, with the targeted maximum rate of 4%.

Third, rotational stability in a minimum of 61 eyes, followed for one year and based on photographic evidence between two consecutive visits at least three months apart or between one month and three months after surgery. The hypothesis test will be conducted at end of one year, with

a targeted goal of achieving 90% of treated eyes rotated less than or equal to 5 degrees between the two consecutive visits.

Fourth, improvement in uncorrected visual acuity, preservation of best spectacle-corrected visual acuity, decrease in refractive myopia and cylinder on higher astigmatism groups of 3.5 and 4.0 diopters, with a minimum sample of 61 eyes, with a one-year follow-up schedule. This endpoint does not have a hypothesis test.

Fifth, visual disturbances evaluated by a patient questionnaire in a minimum of 61 eyes followed for one year. The focusing and severity of glare, halos, blurry vision, double vision, impairment of night vision or difficulty with night driving and visual spatial distortion will be evaluated. There is no hypothesis test mentioned for this endpoint.

FDA believes there will be additional safety endpoints that could be addressed through this post-approval study. For example, the ICL clearance may be reduced with increased age, and association between ICL clearance and cataract formation is unknown.

The proposed study hypothesis targets detecting mean ECD loss rather than the proportion of eyes with large ECD loss. In addition, results on ECD loss from the MICL post-approval study are difficult to interpret because there was no concurrent control group.

The length of five-year follow-up specified in this protocol may not be sufficient to capture long-term cataract formation.

The type of questionnaire to be used for evaluating visual disturbances was not specified. FDA requires the questionnaire to be validated prior to being used in the post-approval study.

Therefore, FDA would like to get input from Panel members on the following:

The TICL study did not assess ECD loss. The MICL post-approval study demonstrated a mean ECD loss of 11% at five years. However, 6% of eyes had ECD loss greater than 30%. The significance of this result is difficult to interpret due to the lack of an active control arm. In light of this, please discuss whether the TICL post-approval study should include an active control arm and be powered to detect significant differences in the proportion of eyes with large changes, such as greater than 30 % loss from baseline.

Please discuss the adequacy of the endpoints in the post-approval study and if there are any additional endpoints or considerations that need to be addressed in the post-approval study, such as ICL clearance.

Please discuss the appropriate duration of follow-up in order to assess safety performance of the device, with specific consideration for late cataract formation in the postmarket setting.

This concludes our FDA presentation. Thank you.

DR. HIGGINBOTHAM: This is Dr. Higginbotham. I would like to thank the FDA speakers for their presentations. To be consistent in our schedule, we will take an additional 18 minutes in the next section to ask

questions, Panel members. And I'll invite the FDA to come to the table to facilitate this Q and A session.

Does any member of the Panel have a brief clarifying question for the FDA? Please remember that the Panel may also ask the FDA questions during the Panel Deliberations session this afternoon or later this afternoon.

Dr. Weiss?

DR. WEISS: Thank you for your presentation. A number of questions. One is does the FDA think there is a different safety profile between the toric and the MICL in terms of endothelial cell loss or any -- or cataract or anything like that? I'm interested in your thoughts.

DR. HILMANTEL: No, we believe that based upon the design of the lens, the safety profile should be the same. The only real difference is that you have that rotational effect --

DR. WEISS: Okay.

DR. HILMANTEL: During surgery, you have to rotate.

DR. WEISS: The other question I have is there were many different axis variables, the 5, the 33, and the 180 that's being asked for. Which one of those do we have enough data to look at and evaluate?

DR. EYDELMAN: Perhaps Don Calogero can answer this question.

DR. HIGGINBOTHAM: Thank you, Dr. Eydelman.

DR. EYDELMAN: Sorry.

MR. CALOGERO: Don Calogero from the FDA. As was mentioned, the initial approval was for four different axes, and our initial evaluation and validation testing was for that. And then we learned later on that they were essentially producing them in additional axes. And the manufacturing process for these is somewhat difficult. So as a result, they don't have clear, or at the time, they didn't have clear QC procedures, such as acceptance rejection, so they would measure each lens, and whatever axis it came out to, they would label it for that. So there's a certain sort of unpredictability back in that manufacturing. It's much improved from today's perspective.

To address your question, at the time of that manufacture for this clinical study, they were attempted to, as they pointed out in their presentation, adhere to 33 different axes, but when we actually look through in terms of what they achieved, I believe our slide indicated there were 80 axes that were actually studied.

So it's somewhat difficult to address your question because of all of the uncertainty.

DR. WEISS: Okay.

DR. HIGGINBOTHAM: Could you repeat that answer?

(Laughter.)

DR. WEISS: Well, now that you've clarified it for me -- and then

I have a final question. So this is clearly a challenging study that has gone on for more than a decade. And so what I'd like to flesh out as a Panel member is three different issues. One, what were the protocol, the original protocol flaws, which I don't think the sponsor can be held accountable for, versus which were the -- versus separating those from protocol deviations which the Sponsor can be held accountable versus changes in terms of improvements with time, which is going to happen in the course of any study that goes on this long.

And so with that, I have a couple of specifics. So no double-blind manifest preop versus postop, that's flawed. Was that part of the protocol? No double-blind looking at the axis rotation, knowing what was put in and then checking it afterwards; that's a flaw, in my opinion. Was that protocol? The transillumination that a Panel member asked about, 9% in the MICL, and then we had the Sponsor tell us 0%, I think they told us 0% in the TICL. Well, that's not possible. I mean, why, if it's a similar safety profile, why would you get 0%? Or that suggests that it wasn't part of the protocol, they weren't looking. So those are just a couple of my questions, and then I'm done.

DR. EYDELMAN: So Dr. Eydelman. I'll start and then I'll defer back to my team.

I just want to clarify the protocol was approved by the FDA. Having said that, in retrospect, there were limitations, and we're going to

come back to each point that you brought up.

And, Maryam, would you like to start?

DR. MOKHTARZADEH: Sure. The first thing I'd like to emphasize is that the protocol for the TICL study was approved prior to approval of the MICL, so as I mentioned in my presentation, there are certain assumptions made about the information we would have to make that decision. That said, given the duration of time that has passed now from the time of the MICL approval, we have much more information about that lens ICL platform.

So you asked about the double-blind -- I'm sorry -- the lack of masking for manifest refraction. And yes, that was part of the protocol. The other things, the other points that you mentioned, as you said, there were some problems with the protocol itself. Lack of standardized methodology for manifest refraction, that is something that wasn't specified in the protocol. That said, there are also sometimes site-specific operating procedures that can compensate for certain parts of a protocol that don't go into a lot of detail. So we did look at all of that.

DR. EYDELMAN: Let me just interject. I believe what Maryam is trying to allude to is some of the limitations are perhaps due to the lack of actually being spelled out in the protocol, and while -- during the approval, perhaps there was a difference of opinion of what that meant.

DR. WEISS: Okay. And the transillumination, why 9% in MICL

and 0 in this or --

DR. MOKHTARZADEH: So the issue, I believe, and Dr. Hilmantel can correct me if he disagrees, is that I presented data from the MICL study cohort when that was included. I do not believe that the data collection was requested at the time of the TICL study, again, believing that the MICL data would provide that information for us.

DR. WEISS: Well, I guess, so as a Panel member also, it makes me question some of the data presented if it's -- if they didn't -- if the Sponsor did not look and was not requested to look, that I understand. But if we're told in the TICL it's 0% transillumination, and it was 9% in the other, then it makes me question the validity of the data, particularly when we're told that every single eye had a deviation from the protocol, which doesn't make the data -- makes one wonder.

DR. MOKHTARZADEH: I understand your confusion. The other thing I would say -- this is in regard to transillumination defects, this is in regard to the endothelial cell loss you described, this is with regard to cataracts. As I described in my presentation, the positioning of the ICL, the sizing, a lot of these factors can affect adverse events, and any differences between how lenses were chosen in the study can affect that. In addition, any changes that are being made in terms of the methodologies being used to size or position these lenses could potentially affect adverse event profiles.

DR. HILMANTEL: Yeah, Gene Hilmantel, FDA. In the toric study, I believe that they did not specifically collect information about transillumination defects. Again, I think they were assuming that they didn't need to collect that safety data because they -- it was based upon the myopia study approval.

DR. WEISS: So I may have misheard, but I thought the Sponsor said there was a 0% transillumination even if they weren't requested --

DR. EYDELMAN: So once again, that's not the data that we're privy to.

DR. WEISS: Got it. Thank you.

DR. HIGGINBOTHAM: Okay. We have a series of interested Panel members. We're going to start with Dr. Chappell with the first question.

DR. CHAPPELL: Rick Chappell. The conversion of TICL diameter from saline to balanced salt solution seems to be an important one. And let me clarify. Was this just an issue during the study, or is it still an issue? That is, any future patients who were to be treated, would they need that same conversion made?

MR. CALOGERO: Yes, Don Calogero. No, it's not an issue anymore. It was an issue, I guess, back in 2004 when we actually discovered that there was a mislabeling in terms of power. We worked with the company in terms of the Myopic ICL for them to correct the labeling, and

then subsequently, in this Toric ICL, it has corrected labeling. And when you correct the labeling, you have to make corresponding change in the power calculator. So that's actually the reason that FDA didn't pick it up earlier.

For the Myopic ICL study, when they actually determined the power constant in the calculator, it's basically determined by clinical data, by regression. So if you've got an error built into your device in terms of power, you correct it by regression in terms of the -- essentially, a fudge factor that's in the calculator.

And as a result, except for the first group of patients, where you're determining the power constant, all of the other patients are really getting the correct power that they need. So even though it was grossly mislabeled, they were getting the correct power.

DR. CHAPPELL: But this fudge factor, as the name implies, has random error built into it. So we were given table 14 in our Executive Summary of a conversion. To spare you having to look it up, it's basically the diameter of BSS is very close to 5% greater than the diameter in .9% saline.

MR. CALOGERO: Yeah, I looked at that --

DR. CHAPPELL: That's on the average, right?

MR. CALOGERO: Yeah, yeah, yeah exactly.

DR. CHAPPELL: And so if I'm a patient, I'm not concerned necessarily with the average, I'm concerned with how much -- for some people, is it 0 and for some 10. So do we have access to the data that shows

how much variation there is in that fudge factor --

MR. CALOGERO: Well, I did look at that, because I did write up a section of the Executive Summary. And when I actually looked at the variation, it was very tight. It was -- and if I'd venture a guess off the top of my head, like plus or minus .1. Say 5% will be 4.8 to 5.2, and that would be, say, 2 standard deviations. It was much tighter than I expected. And when they were coming up with this factor, they did various studies, and based on their sample size -- I don't remember what it was -- say 50 samples, 100 samples, they determined it's this average value plus or minus, as I say, a small variation.

So it's just another potential error in this Toric ICL data. Typically, when you actually manufacture it and you measure the power, it's the power that is going to be in the eye. In this particular case, they did the study, they generated the power in the saline, but now the various errors that we have in power and diameter are a combination of the manufacturing tolerance, there's always a manufacturing tolerance, the measurement of uncertainty of that manufacturing tolerance, plus on top of it, as you're pointing out, this conversion factor --

DR. CHAPPELL: I realize that. And from what you say, the conversion factor is fairly uniform and accurate. I was just looking for a graph to bolster that table, to see a nice straight line. But you assure me that there is one?

MR. CALOGERO: Well, based on my having the similar question, I looked at their raw data, and it seemed fairly tight. And when I looked at the actual power, the difference is based on the variability of that power constant, be .782 equated to, like, a few hundredths of a diopter when you looked at the range.

DR. CHAPPELL: Okay. So I'd imagine the variation involved in measuring it --

MR. CALOGERO: Oh, it's much, much --

DR. CHAPPELL: The biological, the medical variation is much bigger than the mechanical issues involved in this expansion?

MR. CALOGERO: Right. I mean --

DR. CHAPPELL: Okay. Thank you.

MR. CALOGERO: -- your tolerance is plus or minus a ¼ diopter on the measurement.

DR. CHAPPELL: I just didn't see any data on that, so thanks for clarifying that.

MR. CALOGERO: Okay.

DR. HIGGINBOTHAM: Thank you. We have about four and a half minutes for three additional Panel members that have questions. So I would ask for brevity at this point. This is Dr. Higginbotham.

We'll start with Dr. Saheb, followed by Dr. Zabransky and then Dr. Macsai.

DR. SAHEB: Hady Saheb. On slide 97, there appeared to be one patient that became part of the group that had more than 30% rotation because they went from 100% to 99%. So I'm wondering if, if we can pull up the slide. If I understood this slide correctly, is there one patient that became categorized as more than 30-degree rotation at this later stage, or are we believing this is related to measurement? So, again, is this related to measurement or a delayed rotation of the lens?

DR. HILMANTEL: I'm sorry. I'm not clear on your question.

DR. SAHEB: So in the fourth row, the less than 30 degrees, it changes from 100% to 99%. So does this mean that there is a new patient that became more than 30-degree -- more equal to 30-degree rotated at 12 months? And if so, do we remember anything else about that patient? Is this going from, you know, 29 to 31 at that stage, or is this what we believe is a delayed rotation of the lens?

DR. HILMANTEL: I don't believe it was a delayed rotation. I'd have to look it up, though, to give you a definitive answer. I honestly just don't remember. My name's Gene Hilmantel. Thank you.

DR. EYDELMAN: Hi, Dr. Eydelman. We can get back to you on that after lunch.

DR. SAHEB: Thank you.

DR. HIGGINBOTHAM: Dr. Zabransky?

DR. ZABRANSKY: Question. To deviate from where we've been

here, it has to do with good manufacturing process, the GMPs that are required by FDA. Apparently, from my perspective, these lenses, you would need a multitude of lenses based upon number of axes, power, size. How is this being controlled? Is the FDA satisfied with the inspections that have come about, especially during the study process, and now, if it is approved, is the GMP going to be -- inspections going to be satisfied?

DR. EYDELMAN: This is Dr. Eydelman. I just asked one of our colleagues from the Office of Compliance to address this.

MR. PEREZ: Hi, how you doing? My name is Cesar Perez. I'm in the Office of Compliance. The firm was -- the manufacturing side that was located in Switzerland was inspected in September 2013, and the inspection was classified by us as VAI, which means voluntary action indicated. We found three observations. It didn't reach the level of a grievous OAI, but we believe that still does -- observation needs to be -- a review or responded to -- we haven't received any response at this moment from the firm.

DR. ZABRANSKY: This not only applies to the manufacturing but also the storage and the distribution at one point, so --

DR. HIGGINBOTHAM: Thank you.

Dr. Macsai?

DR. MACSAI-KAPLAN: I want to follow up a little bit on what Dr. Weiss asked. And thank you for the great presentation. But I'm confused.

(Laughter.)

DR. MACSAI-KAPLAN: So the Sponsors talked about an error from 1.5 to 1 diopters on their protocol deviation. Was that a protocol deviation or was that a protocol flaw? In other words, was that piece of paper reviewed by the FDA before the trial was started and approved, or was that a mistake? That's question number one. Should I give you all of them or --

UNIDENTIFIED SPEAKER: No.

DR. MACSAI-KAPLAN: Okay.

(Laughter.)

DR. MOKHTARZADEH: This is Dr. Mokhtarzadeh, Maryam Mokhtarzadeh. I'm going to begin the response, and then I believe Dr. Gene Hilmantel may jump in. First of all, I'd like to say that when we review an IDE, we're looking at the protocol. We're also looking at a number of other pieces like manufacturing and other specifications about the ICL. So that's one thing. So the lens specifications are mentioned sometimes in different parts of an IDE submission, not just within the protocol itself.

The other thing I'd like to mention, again, before directly addressing you, is that in every case, emmetropia is not necessarily being targeted. So a statement like that doesn't necessarily indicate to us that the Sponsor has made a typo, if you understand what I'm saying. So in evaluating that, we have to do based on what we saw in the IDE, what lens parameters

were approved, what we were allowing -- what we were approving for the Sponsor to begin a study for. And the investigational device, as we understood it to be, is what I put on my slide. Those are the parameters we understood they were going to be investigating.

DR. HILMANTEL: Gene Hilmantel. So this has to do with optics more than anything else. There is not, contrary to some misconceptions, there is not a one-to-one correspondence between the ICL cylinder power and the refractive cylinder power that you want to correct. So in the protocol, the Sponsor said that they were going to correct a range of 1 to 4 diopters of refractive cylinder. That was the range in the inclusion criteria based upon the phoropter measurement of manifest refraction. There's not a one-to-one correspondence between that and the toric ICL cylinder power.

So when the Sponsor says they made a mistake, that that should have corresponded, it just doesn't correspond. People who have a 10-diopter correction are going to need a different cylinder power than people who have a 3-diopter spherical correction. So all we know is that in the IDE protocol, they said the inclusion criteria of 1 to 4 for manifest refraction, but they also submitted that they were requesting approval for from 1½ diopters of toric cylinder power, TICL cylinder power, to -- what was the maximum?

MR. CALOGERO: I believe it was 6 in the original.

UNIDENTIFIED SPEAKER: I believe it was 6.

MR. CALOGERO: Six.

DR. HILMANTEL: Yeah, it was --

DR. MACSAI-KAPLAN: My second question is, I'm a little confused on, does the Agency feel that from the data in the MDR or the literature published since the MICL approval, that there is reason for substantial concerns of safety or efficacy such that there has been a labeling change or a recall?

DR. EYDELMAN: So there has not been a recall. We're here discussing TICL, but as you have heard, the TICL study was designed in a way that it was presumed the safety data will be obtained from MICL. So, inherently, we're here today reviewing all of the data. And subsequent to this Panel, we will be making decisions.

DR. HIGGINBOTHAM: Thank you, Dr. Eydelman.

DR. MACSAI-KAPLAN: The third part of my question is that the rotational stability is just really confusing. You guys have numbers on your slides of 13 eyes for greater or equal to 15 degrees. Then on another slide, 16 eyes greater than or equal to 15 degrees, 6 eyes greater than 30 degrees. So like my colleague, I'm really confused by that data. So if you could somehow make it less confusing, that would be helpful.

DR. EYDELMAN: We will attempt after lunch.

DR. HIGGINBOTHAM: Given that we are at a moment where we should break for lunch, I'd like to thank the FDA for their presentation and the Panel members for a very good discussion.

We will now break for lunch. Panel members, please do not discuss the meeting topic during lunch amongst yourselves or with any member of the audience. We will reconvene in this room promptly at 1:15. I will ask that all Panel members please return on time. Please take any personal belongings with you at this time. You will not be allowed back into the room until we reconvene. But just to confirm, is the room going to be secure? Do we know that? So we can leave belongings? Okay. Thank you. 1:15.

(Whereupon, a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:19 p.m.)

DR. HIGGINBOTHAM: Members of our Panel now assembled. It's about 1:19 now, so we will now proceed with the Open Public Hearing portion of the program. I'd like to resume the meeting. We will now proceed with the Open Public Hearing, as I mentioned. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda. Ms. Facey will now read the Open Public Hearing disclosure process statement.

MS. FACEY: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such a financial relationships. If you choose not to

address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. HIGGINBOTHAM: For the record, all Panel members have been provided written comments received prior to this meeting.

For today's Open Public Hearing, we have received seven requests to speak. Each scheduled speaker will be given five minutes to address the Panel. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting. The Panel appreciates that each speaker remains cognizant of their speaking time. And as Chair, I will interrupt you if you are going over. So please be cognizant of that. Five minutes is the time limit.

We have seven speakers. I will list them, and I would ask you to come up in the order that I read your names. We will begin with Dr. Manus Kraff, Professor of Clinical Ophthalmology at Northwestern University, and private practice. He will be followed by Dr. David Schneider, Director of Midwest Eye Center in Cincinnati, Ohio. He will be followed by Dr. Lauren Doamekpor from the National Research Center for Women and Families; Dr. Paul Harton from the Harbin Clinic Eye Center, Rome, Georgia, Dr. Gregory Parkhurst from Parkhurst - NuVision, Mr. Richard Ferguson, and then, finally, Dr. Paul Dougherty from the Dougherty Laser Vision and an instructor at UCLA Jules Stein Eye Institute.

Dr. Kraff?

DR. KRAFF: Thank you. I would like to state that I have no financial conflicts of interest in any of the statements I am about to make. STAAR Surgical did compensate my expenses for this trip to Gaithersburg, Maryland.

I am Manus Kraff, a practicing ophthalmologist from Chicago, and a Professor of Clinical Ophthalmology, Northwestern University, Chicago, Illinois.

I am very fortunate to state that I am in my 53rd year of practicing ophthalmology, both in the clinic and in surgery. My 53 years have enabled me to participate in a wide evolution and revolution of products and services.

Fifty-three years ago, cataract surgery involved intracapsular cataract extraction with a capsule forceps or an irisophake followed a few years later by cryoextraction and a year or two later by alpha-chymotrypsin. There was always a moment of truth as the crystalline lens exited the eye. Postoperative patients were then presented with aphakic spectacles, with all of their inherent problems, followed soon with the Welsh 4-Drop spectacle lens, sclera contact lenses were available, and corneal contact lenses were still a few years away. Intraocular lenses, while being experimentally available in Europe, were much discouraged by academia in the USA. In a few years, a very radical procedure named phacoemulsification would raise its ugly, later termed elegant, head.

It was now year 10 on our time scale for me. About this time, the very early pioneering ophthalmologists from Europe and the Soviet Union brought intraocular lenses to our shores. Now the management of phacoemulsification and intraocular lenses could take place. The evolution from intracapsular to extracapsular cataract surgery could now proceed. And the intraocular lens could move from the anterior chamber to the posterior chamber where the human crystalline lens evolved.

Refractive surgery was the next revolution I would encounter. RK began approximately year 17 on our time scale. I didn't participate in RK, as I had visited Professor Fyodorov in 1980 in the USSR and was underwhelmed with the procedure. RK didn't last long, as a newer evolution was taking place, excimer laser visual correction. When PRK, photorefractive keratectomy appeared, I entered very enthusiastically after viewing Marguerite McDonald's first patient in New Orleans in 1989. By 1991, year 31, I was part of the VISX Excimer Laser Phase II cohort of investigators and appeared before this group in 1994 and 1995 to testify for the procedure and the laser, which was approved in 1996, year 36.

My first exposure to the ICL was in 1993, year 33, when asked to go to Russia. My second trip to the USSR, now being called Russia, by STAAR Surgical -- the trip and expenses were compensated -- and evaluate Professor Fyodorov's study with a posterior chamber phakic intraocular lens for the treatment of high myopia. Spending a week evaluating preoperative

and postoperative patients, as well as observing live surgery, convinced me that there was indeed a place for our expanding armamentarium for this lens.

I became involved in the clinical trials, traveling to Argentina in 1996, at STAAR's expense, to observe patients, practice surgical technique, and participate in wet labs, and to the Dominican Republic in 1997 to perform live surgery. I participated in Phase II and III of the FDA clinical studies starting in January 1998, year 38, with my first ICL procedure.

I have now implanted well over 100 ICLs. My next statement will be anecdotal, but relevant. In medicine --

DR. HIGGINBOTHAM: Twenty-seven seconds.

DR. KRAFF: -- there is always a place for anecdotes. Now in my 16th year of implanting ICLs, year 53 in our journey, I have yet to experience one patient who has experienced a corneal decompensation for progressive endothelial cell loss. I know this issue has been of interest to the FDA. Certainly, in that period of time, I would have expected to encounter at least one patient with this condition if it were of significant clinical relevance. I have not encountered that patient yet.

The Toric ICL for the correction of myopia and astigmatism is another ICL, a worthy addition to our armamentarium, a reality whose time has come and has arrived for ophthalmologists in the USA.

I wish to thank the Panel for permitting me to take you on this 53-year journey today and hope to again return in 53 years for an update.

Thank you.

(Laughter.)

DR. HIGGINBOTHAM: Thank you, Dr. Kraff.

Our next speaker, Dr. Schneider.

DR. SCHNEIDER: My name is Dr. David Schneider, and I'm here to represent the patients in whom I have personally implanted these lenses. I am not being paid by STAAR to be here, though they have covered my travel and lodging expenses.

I was one of the principal investigators in the Toric ICL FDA study. I have been involved as an investigator in several FDA trials, and the Toric ICL definitely is the outstanding optical device that I have had the pleasure to implant. I had hoped to bring one of my patients in particular, but he has recently gained employment and did not want to risk his new job by asking for time off in the initial probationary period. So he wrote a little summary about himself, which I would like to read at this time.

"My name is Michael G., and I was born on October 7th, 1971 in Covington, Kentucky. I had a relatively normal childhood until age 6, when I contracted meningitis, which nearly killed me, and left me deaf in my left ear and close to deaf in my right ear. I lost almost all of my balance and had to learn to walk and talk again. At age 10, my vision worsened, and I was taken to an eye doctor and fit with glasses. In my late teens, I began wearing contact lenses, and because of my extremely poor eyesight, they were thick

and cumbersome, and they would often pop out.

"When I would lose a contact lens, it left me unable to see effectively. My father encouraged me to attend a university in Washington, D.C., where I learned sign language and did very well academically. My hearing loss is permanent, and I have always worried about my well-being and safety while wearing contacts. If I was stranded and lost my contacts, I worried about the ability to defend myself or survive.

"I searched for a solution and was referred to Dr. David Schneider at the Midwest Eye Center in Cincinnati, Ohio. It was there that I was told of an artificial lens procedure that was approved internationally but not in the United States. Dr. Schneider petitioned the FDA on my behalf for a compassionate waiver. Months later, I was thrilled to learn that the FDA had approved the waiver and would allow me to have this surgery. Dr. Schneider did one eye at a time, allowing six weeks between the surgeries. I used eye drops to heal, and when I first opened my eyes, I was amazed. I had perfect vision and what I call eagle vision. It was truly life changing.

"One night after the surgeries, I had pulled my car over to the side of the road to retrieve something from my trunk. Out of the woods in darkness, a man appeared asking me for money and pulled out a gun. I began to feel uneasy and attempted to get back into my car and leave. At that time, a second man jumped onto my back and began hitting me. The

man on my back was armed with a hunting knife, and he tried to cut my throat, and when that didn't work, he inverted the handle and smashed it into my left eye, virtually blinding me in the left eye. I was able to break free and run to my car. They fired gunshots, which missed me.

"I drove to a local hospital, where I was treated for a deep knife cut to my left hand. My hand was stitched up. My nose had been broken in two places. I was told I need to have my left eye checked out as soon as possible. I returned to Cincinnati, Ohio, where Dr. Schneider surgically repaired the damage to my left eye in a very brief procedure.

"I am now 42 years old, and the surgery has changed my life in so many ways. Before the surgery, I had to wear thick glasses or contacts, and without them, I could not see with clarity. Basically, all I saw were shapes. I was not blind, but I was pretty close to it. After the surgery, it was simply amazing that I could see both far and near with incredible clarity.

"I now have remarkable peripheral vision, and the difference is night and day. My new vision allows me to live and travel with confidence, and I now have a greater sense of security and lead a more independent lifestyle. I hope that my story helps you in deciding to approve this lens surgery for the many Americans who would benefit. Corrective glasses and contact lenses on the eye were state-of-the-art years ago. But now modern technology has made it possible to move to the next phase by placing a new lens in the eye.

"We must continue to progress in medicine, and this surgery dramatically improves vision and one's quality of life. I very strongly urge you to approve this procedure."

In closing, I would like to relate something that happened just last week -- first, I'd like to say that the procedure that I did on this gentleman, he had a traumatic injury to the eye, which slightly caused one of the haptics to come up from behind the iris. I was able to go back in, just redeposit it and without any problem, did not have to rotate the lens. The lens remained stable astigmatically.

In closing, I'd like to relate something that happened just last week. A 40+ year old mentally challenged patient in whom I was given a compassionate waiver to implant the Toric ICL years ago happened to come in for her annual exam. She was, as always, accompanied by her parents. She gave me a big hug in the hallway upon greeting me and was grinning from ear to ear. Her exam was again fantastic, and I told the family to return in a year. I also mentioned that I would be coming here to talk about the Toric ICL. They exited --

DR. HIGGINBOTHAM: Twenty-five seconds.

DR. SCHNEIDER: -- and I went back to see another patient. Then her father wandered back alone and stood in the doorway and said to me, with tears streaming down his face, "Please tell those people to approve this lens. It has given our daughter her life back and changed all of us in this

family. It has truly been a gift of God." Here was a 73-year-old man crying with joy and gratitude and hope. That is the impact this technology has on people's lives. I hope you will bear that in mind when you make your recommendations. Thank you.

DR. HIGGINBOTHAM: Thank you.

Dr. Doamekpor?

DR. DOAMEKPOR: Good afternoon. Thank you for the opportunity to speak today. My name is Lauren Doamekpor, and I'm a senior fellow at the National Research Center for Women and Families. Our nonprofit research center assesses medical and scientific data and provides objective health information to patients, providers, and policymakers. Our organization does not accept funding from medical device companies, and therefore, I have no conflicts of interest.

We carefully reviewed the data provided to you by the FDA and want to share our research and ethical concerns. Myopia and astigmatism are extremely common, and we approached today's meeting with hope that the evidence would be solid so that people could benefit from this device. I'm sure you did, too.

However, we have two substantial concerns that have already been mentioned in today's meeting. We have reservations about the effectiveness of the device. There are many methodological problems. The study's protocol deviations include device modifications, the use of

invalidated survey tools, unstandardized methodology, out-of-window visits, as well as missing data. Although the Sponsor attempts to address the out-of-window visits by conducting comparative analyses, the analyses do not take into account other deviations that may introduce bias. That makes it impossible to draw conclusions about the effectiveness of this device.

Unfortunately, the Sponsor has a history of violations for this clinical study, including the initiation of a study protocol without FDA approval. The Sponsor has clearly shown little respect for the approval process. For that reason, I don't think we can give the benefit of the doubt about the various methodological shortcomings and violations in this study.

Second, we are concerned that endothelial data was not collected in the Toric ICL study. That was absolutely essential to assess the long-term safety of this device. The FDA's review noted that the Sponsor's previous Myopia ICL post-approval study showed that 6% of eyes experienced significant endothelial cell loss between four and six years after surgery. Loss or destruction of endothelial cells is permanent. And significant loss can lead to corneal edema or blindness. Would you be willing to take that chance if you knew about it? Would your patients appreciate your recommending this device if it causes blindness a few years later?

The Sponsor proposes to collect data on endothelial cell loss in post-approval studies. Think of the millions of Americans who would be harmed by this device in the meantime. Unless we have better long-term

data to warn patients of the exact risks, putting this device on the market would be unethical, and it could certainly harm the patients' trust of the FDA and ophthalmic surgeons.

Researchers at major medical schools across the country have studied the track record of companies in complying with FDA's postmarket study requirements. Unfortunately, it's clear that companies take their time in doing postmarket studies and often fail to provide the incentives needed to keep patients from dropping out of longer-term studies.

Please protect patients and the reputation of the FDA by voting to require follow-up of the TICL cohort before this device is approved.

Thank you.

DR. HIGGINBOTHAM: Thank you.

Our next speaker is Dr. Paul Harton.

DR. HARTON: Dr. Higginbotham and members of the Panel, good afternoon, and thank you for granting me the opportunity to address you today.

My name is Paul Harton, and I am a board-certified ophthalmologist from Rome, Georgia. I would like to disclose that I have no financial interests in STAAR Surgical or the Visian ICL. STAAR has paid for my transportation and room related to my appearance today.

However, while it is true that I am here at the request of STAAR, I am not here on their behalf. Instead, I appear before you on behalf

of my patients, the many patients, both in my practice and around this great country, who could benefit from a toric version of the Visian ICL.

I started practicing ophthalmology at the completion of my residency in 1995. Soon afterward, excimer laser vision correction became available in the United States. This laser technology was clearly the biggest advance in ophthalmology in decades. While thousands of my patients have benefited from laser vision correction over the many years, many could not take advantage of this technology for a variety of reasons, such as inadequate corneal tissue or abnormal topographies.

The FDA approval of the Visian ICL for myopia in December of 2005 gave hope to many of these patients who desired surgical correction of their nearsightedness. Patients previously thought to be poor candidates for corrective surgery were now good ones.

In February 2006, I became the first ophthalmologist in Georgia to implant the ICL after approval by the FDA. Interestingly, within the last week, I saw one of those initial patients for an eight-year follow-up examination. She continues to be thrilled with her vision and her lifestyle, rid of the burdens previously imposed by 12 diopters of myopia.

Initially, I used the ICL as a niche product, implanting mainly in those who could not have laser vision correction surgery. As I became more familiar with the product, an impressive thing occurred. I found myself more often recommending the ICL as an alternative to laser vision correction, even

in patients who were good candidates for LASIK and PRK. My reason for this evolving thought process was fairly simple. The ICL was providing my patients with superb uncorrected visual acuity while maintaining an excellent profile. The results were more stable postoperatively than LASIK, and the quality of vision was excellent. In short, the ICL quickly proved to be a safe and effective tool for correcting all levels of myopia.

The ICL has continued to evolve in my practice to a point where we offer it as an option for all patients who are candidates regardless of whether they are also laser correction candidates or not. We have even had patients who are candidates for both select the ICL over LASIK for a variety of reasons.

While hundreds of my patients have benefited from this remarkable technology, many more with significant astigmatism have had to wait. These astigmats are less than ideal candidates because they often have enough residual refractive error after a Myopic ICL implantation that they'll still require corrective eyewear. Currently, their only surgical option is to perform additional laser or other corrective corneal surgery to correct the residual astigmatism. However, this subjects the patient to a second surgery, and they are also not great surgery candidates on the cornea anyway, so many of them opt to do nothing.

On three occasions, I've gone to Europe to attend the annual European Society of Cataract and Refractive Surgeon meeting. I've spoken

with ophthalmologists from around the world who have had the Toric ICL available to them for years. It is clear that the Toric ICL is a safe and effective tool to help an even greater number of their patients become less dependent on corrective eyewear.

Now, I understand that the FDA is charged with protecting the interests of Americans with respect to new drugs and devices. What is good for Europe and Asia is not always in the best interest of the United States. However, we really are not talking about a new product here. The ICL has shown itself to be safe and effective in the treatment of myopia in the United States. The toric version is simply an optical modification of the currently available myopic version, not a whole new product.

The fact that we can also look to our colleagues elsewhere for a track record is simply a convenient truth. The toric version of the ICL has shown to be safe and effective on several continents for the correction of myopic astigmatism.

As I stated earlier, I'm here on behalf of my many American patients who could benefit from the availability of a toric version of the ICL. I have in my office a list we have compiled of over 200 patients who are potential Toric ICL candidates. Instead of having two surgeries, these patients have elected to wait for the Toric ICL to be approved in the United States. Some have waited for seven years.

I'm respectfully requesting, or pleading, on their behalf that the

Panel favorably vote on the Toric ICL today so that we can move closer to giving our patients this technology that is currently available in over 60 other countries.

In closing, members of the Panel, I greatly appreciate the opportunity you have given me today to speak on behalf of my patients and similar patients throughout our great nation. Thank you for your time.

DR. HIGGINBOTHAM: Thank you.

Next we have Dr. Parkhurst.

DR. PARKHURST: Thank you for the opportunity to present to this distinguished Panel today. My name is Greg Parkhurst. I'm a practicing ophthalmologist in Texas.

I implanted my first ICL back in 2007, and it was actually part of a humanitarian project in the Dominican Republic. Many patients there are poor. They don't have access, even as children, to any type of vision care. So many of them grow up extremely myopic or may have astigmatism with no access to glasses or any type of vision improvement. So many of them grow up amblyopic. We had an opportunity to implant Toric ICLs for some of these people, and it was a tremendous opportunity to see what a difference it could make in quality of life.

So that was my first ICL. But most of my experience comes via participation in the Warfighter Refractive Eye Surgery Program for the United States Army. Since I began implanting, I've now performed over 1,000 ICL

procedures.

Many Americans, but especially first responders, need a better vision solution than those currently available. Observe the photograph of this pair of spectacles on the slide here. So, you know, we see some of these pictures about, you know, graphs of 20/20 versus 20/15, but do you really know what it's like to be -19 myope. This is not an ideal solution. These are spectacles that are heavy. They do not provide good quality of vision. And especially for first responders, they are not an ideal option.

I'd like to share with you a story about my second-most memorable patient at this time, and in a few minutes I'll tell you about my number one most memorable patient. But my second-most memorable patient is a Houston fireman. This is a patient who was -19 diopter myope, and he told stories of how in the middle of the night, the bell would go off, and he'd have to fumble around to try to reach for his -19 spectacles, and it provided a safety hazard for him. After we were able to perform this vision correction procedure using the ICL, he was able to better perform his duties and fight fires in Houston.

So first responders, and especially military service members, have a very unique reason to have refractive surgery. We know that glasses and contacts and LASIK all have limitations, and for this reason, the military has been using refractive surgery as a technique to make our soldiers better able to defend our country. Now, over 800,000 eyes have been treated as

part of the Warfighter Refractive Eye Surgery Program. Two of those are my own. And the Army has been publishing data on the safety and efficacy of a variety of procedures, including PRK, LASIK, and ICL procedures.

My Texas patient population consists of many service members from Fort Hood, Texas. The center there is performing about 4,000 procedures on an annual basis in order to make our troops more ready to deploy. We've published the results of ICLs in those patients, and the results are astoundingly good. In fact, in a consecutive case series of 139 eyes, we achieved a 20/20 uncorrected visual acuity rate by three months postoperative in 96% of eyes. Two-thirds of eyes were 20/15 uncorrected. Only six eyes did not achieve at least 20/20 uncorrected visual acuity in our analysis, and guess what they had? Astigmatism. That's the reason that we're here today is to be able to help these patients who not only have myopia but also astigmatism.

Part of the additional studies that we've done have looked at safety in this particular patient population. This is a patient population that's different than the one that you have before you today. These are patients that are constantly in harm's way, running through smoke, rain, fog, dust, and have potential exposure to significant trauma. We've had very few complications in our dataset, with zero retinal detachments, zero cases of endophthalmitis, zero cases of postoperative CME, zero cases of traumatic lens dislocation, zero cases of corneal decompensation, and very, very few

cataracts. So the conclusion after our first published analysis is that ICLs are a safe and effective alternative for laser vision correction for soldiers.

The next thing we looked at is relative to quality of vision, and one of the questions brought up this morning was regarding potential for vision quality issues with a toric lens implant. Vision quality is very important especially with military service members. And one of the things that we looked at is night visual acuity. And we set up an IRB controlled prospective study comparing our best laser vision procedures to the ICL and particularly looked at night vision and contrast sensitivity under a night vision goggle environment. Many of the night vision goggles that are worn present a green background like you've probably seen in videography. All of the results that we saw from this showed significant improvement in night vision and night contrast sensitivity with the ICL, which was not seen in our LASIK patients.

DR. HIGGINBOTHAM: Thirty seconds.

DR. PARKHURST: So we were able to prove excellent optics with this technology. However, the main limitation to these studies is that we had to measure them under best-corrected circumstances. We had to adjust for the astigmatism in order to see what the optical results were. But we know that for these types of patients, the goal is not to be wearing spectacles, but spectacle independence.

The risk/benefit analysis for myopic astigmatism is complex. We need to take into account the short- and long-term risk of all options,

whether they be glasses or contact lens wear on the cornea or refractive surgery. My current status in Texas is that I now have a big file cabinet of patients, Texas citizens, and military service members awaiting approval of the Toric ICL. I've also cared for many Americans who have already gone overseas to gain access to this technology, and I've taken care of them on the postop side.

I already told you about my second-most memorable patient. This is my first. This is my wife. She's a successful ICL candidate --

DR. HIGGINBOTHAM: Please close.

DR. PARKHURST: -- patient from five years ago. She had the procedure when my daughter was one year old. Americans deserve FDA approval of the Toric Implantable Collamer Lens.

DR. HIGGINBOTHAM: Thank you.

Next we have Mr. Richard Ferguson.

MR. FERGUSON: Yes. My name's Richard Ferguson, and I'd like to state for the record that I'm not being paid by STAAR Surgical to be here. However, they have compensated me for my travel.

It is a true honor that I have the opportunity to speak before you all today. I am here to speak on behalf of my son, Matthew. When Matt was four years old, my wife and I noticed that he was experiencing difficulty watching television. We had him examined, and the doctor informed us that he needed glasses. I asked him how bad his vision was, and he said, "Let me

put it to you this way. He probably has never seen you or the leaves on the trees." You can imagine how we felt as parents. Matt suffers from a severe case of myopia with astigmatism. Even though we had gotten Matt glasses, he had already developed a learning disability due to his poor vision. The school district was not able to provide the services that Matt required, so they bused him to a special institution 20 miles away every day. This broke our hearts as parents, but we knew we were getting the best for Matthew. Matt attended this institution for six years until he graduated high school.

Matt has always dreamed about pursuing a career in law enforcement, but first serving his country in the armed forces. He wanted to be a soldier first and foremost. In 2011, Matthew enlisted in the Army, but during the physical examination, he was disqualified because of his eyesight. The Army sent him for an independent evaluation, where the doctor concluded that Matt was fit to serve in the military. The Army overrode the doctor's recommendation anyway and disqualified Matt from serving. Matthew was devastated but never gave up hope.

Matt decided he was going to try to have his eyesight corrected by means of surgery. We went to several physicians for consultation, the last being the Massachusetts Ear and Eye Clinic in Boston. The doctors concluded that Matt was not a candidate for LASIK because too much tissue would be lost during the procedure. They suggested that we wait for this lens called the Toric Visian ICL. The doctor advised us that the

FDA was expected to approve the lens within two months. It has been over five years since then.

During this time, I researched the Toric ICL extensively and determined that this was the correct and safest procedure for Matt. I then contacted the FDA on numerous occasions to no avail in an attempt to determine if the lens had been approved. I have also reached out to numerous doctors and U.S. senators seeking information on why this approval procedure has taken so long. Only one senator responded, advising me that protocol needed to be followed. I agree. I believe in protocol, but I think we can all agree that 5+ years is excessive.

Today, Matthew has found a way to preserve regardless. He is currently enrolled in college and maintains a 3.3 GPA. He is also in the Army National Guard and is employed as a correctional officer with the State of Connecticut with hopes of becoming a state trooper once he has his vision corrected. This is my son Matthew today.

I am here today to ask you all to vote to have the FDA approve the Toric Visian ICL. I ask this for two reasons. The likelihood that Matt's battalion will be deployed to Afghanistan in the near future is real. As a father, I would like my son who has worked so hard and who has overcome so many challenges in his life to be able to be on a level battlefield with the enemy. In other words, I'd like my son to be able to see the enemy before the enemy sees him. I believe that if my son is willing to put his life on the

line for us, considering all the hurdles he has faced in his life, the least we can do is provide him with better eyesight so that he can meet the challenge in time of war.

Secondly, this is not just about Matthew. It is also about thousands of other men and women that have struggled with similar eyesight as Matt's, people who seek a better life, clear vision, and individuals that have waited so long for the opportunity to pursue their dreams, and after so long, just the possibility to simply see, something most of us take for granted, myself included.

I was blessed to have 20/20 vision my whole life. When I turned 50 and required reading glasses like these, I thought my life had come to an end. Then I realized that this was just a small sample of what Matt and others experience daily and how fortunate I was to have had normal vision for all those years. I recalled what the doctor said about Matt's vision at age four. It made me realize how Matt and others like him have struggled their whole lives never being able to see clearly --

DR. HIGGINBOTHAM: Thirty seconds.

MR. FERGUSON: -- not for even one day, one hour, or even one minute.

In conclusion, I ask that you all vote in favor of having -- again ask that you all vote in favor of having the FDA approve the Toric Visian ICL. I ask that you think about the thousands of individuals whose lives you could

change here today.

Thank you so much for allowing me to travel here today to tell Matt's story and for allowing me to be an advocate for those individuals who walk every day in Matt's shoes, who deserve a break, and who want nothing more than to chase their dream and to be as productive and successful in life as they can be.

Thank you.

DR. HIGGINBOTHAM: Thank you.

Dr. Paul Dougherty?

DR. DOUGHERTY: Does that work? Thank you so much. I'm Dr. Paul Dougherty. I'm a lens and laser-based refractive surgeon from southern California, and I have no financial interests to disclose except STAAR did pay for my travel. But like Dr. Harton, I'm here on behalf of my patients, okay? This is the right thing. This lens is safe and it's effective.

I began implanting this lens in 1999, and since then, I've implanted well over a thousand lenses and have changed incredible numbers of lives. I initially got involved with this technology when I saw how poorly patients did with high myopia with LASIK, which is an approved technology for high myopia. I began implanting these lenses internationally in Mexico, and then I became part of the FDA study of the lens.

Subsequently, I've gotten such great outcomes that I preferentially put in ICLs for patients that are great LASIK candidates,

including close friends and staff members, related to the safety and effectiveness of this lens.

I've been absolutely thrilled with my outcomes and, again, have helped countless numbers of patients gain good vision without glasses and contact lenses when they really have no other option. And that's both for patients that were good candidates for LASIK as well as those that weren't.

And there is really a huge unmet need for myopic astigmats who are not good laser vision correction candidates who are really being denied the ability to see well without their glasses with a product that's identical to a currently approved product. Currently, half the patients that I perform Visian ICL on have visually significant astigmatism, meaning I'm putting them through two surgeries. I'm doubling their risk when I help them. I have to do limbal relaxing incisions at the time of surgery, LASIK before surgery, or PRK six weeks after surgery in order to get them the vision that they deserve. And it's really not fair to patients to put them through two risks when there's this product on the market that's safe and -- or that's available that's now safe and effective.

Next I'd like to comment on the safety profile of the Visian ICL in my hands, which has been excellent. I've had zero cases of corneal decompensation in 15 years, with well over a thousand cases. I've had no cases of chronic glaucoma. I've had a less than 1% rate of cataract formation, with most of these patients being over age 50. And most of the cases I've

had to do cataract surgery on are patients that have age-related cataracts, nuclear sclerotic and posterior subcapsular cataracts. I don't run into anterior cortical cataracts that often. And the patients that I do the cataract surgery on who develop cataracts all do great. It's cataract surgery. It's a 20-second maneuver to remove the ICL and take out the cataract. Anecdotally, patients under 40 simply don't get cataracts.

I'm actually in the process of publishing data that I've looked at. It's 104 consecutive eyes of patients followed for up to five years looking at complications. My rate of cataract is zero. My rate of corneal decompensation is zero.

So, in summary, the toric version of this lens is basically the myopic version that's already been approved, with a simple optical modification. And there's been a lot of discussion today about risks of this lens. The risks of this lens are identical to the risks of the Myopic ICL, which are low. Again, in 15 years, doing well over a thousand cases, I just don't run into problems. Occasionally, I see a cataract, most commonly age-related.

So what I'm asking you to do as the FDA Panel is do the right thing and approve this lens. In my hands, it's been very safe and effective. We know there's an unmet need for this lens. And the safety profile is identical with this lens as the currently approved myopic lens. So, again, I ask you to please vote for approval of this lens.

Thank you so much for your attention.

DR. HIGGINBOTHAM: Thank you. That completes our listed audience members who would like to actually provide a testimony. Is there anyone else in the audience who would like to actually present a testimony? You'll have three minutes to do so.

(No response.)

DR. HIGGINBOTHAM: Seeing no one rise from their seats, we will now close this open public hearing session.

Is there a Panel member who would like to ask anyone a question from the public?

DR. WEISS: Well, I wanted to say we also received in our packet an additional letter from someone in the public, so I don't know if that has to be put into the proceedings.

For those surgeons who had done a large volume of these, I was wondering what -- do you have any estimate of second surgical procedures in the first year to compare to the data that we are looking at from this study, in terms of needing to go back in the first year?

DR. DOUGHERTY: Happy to comment on that. The only time I have to go back is when somebody has a residual cylinder that I wasn't able to get with a very inaccurate limbal relaxing incision. I don't do exchanges. I don't do -- I mean, you put them in, and you don't have to go back. You really don't. The only time I remove ICLs is when patients -- and they're typically the patients that were early on in the FDA study who are now in their 60s and

have age-related cataracts.

DR. WEISS: So would you say there's a learning curve, then --

DR. DOUGHERTY: Early on, there is a little bit of a learning curve with this lens just like there is with cataract surgery. But the bottom line is, in experienced hands, this is a very safe and effective procedure.

DR. WEISS: Do you have an impression what you would need to get experience, because that would be helpful to the Panel?

DR. DOUGHERTY: Well, honestly, if you're a cataract surgeon, it's identical in terms of the skills that are needed, and I really don't think there's much of a learning curve from the standpoint of cataract surgeons, because it's the same surgical skills.

DR. WEISS: Other question, which you may choose to answer or not choose to answer, but what is the -- is there an approximate price differential from the out-of-pocket cost to the patient for your most premier LASIK laser vision correction procedure versus the ICL?

DR. DOUGHERTY: Oh, absolutely. This is a premium procedure. You get better vision with this lens. It's one of the reasons that when my patients come into my office --

DR. WEISS: I'm talking price, cost to the patients --

DR. DOUGHERTY: Price, we charge more.

DR. WEISS: Can you tell me how much more?

DR. DOUGHERTY: We charge -- well, it depends on the level of

refractive error, but somewhere in the neighborhood of $500 to $1,000 an eye more for the implantable lens --

DR. WEISS: Okay. Thank you. Thank you very much.

DR. PARKHURST: Can I answer the first question as well?

DR. WEISS: Either one you'd like.

DR. PARKHURST: Sure.

DR. WEISS: Thank you.

DR. HIGGINBOTHAM: Please state your name.

DR. PARKHURST: Dr. Parkhurst here. I also have a lot of experience implanting the ICL. And you asked the question in the first year, what's the approximately percent of reop or reintervention. It's less than 1% for me.

DR. WEISS: Okay. Thank you.

DR. CHAMBERLAIN: Dr. Parkhurst, you mentioned a very low cataract rate. Win Chamberlain. Can you give us a number on that and if any of those patients required intervention?

DR. PARKHURST: I've had three patients with bilateral cataracts with over a thousand ICLs. All three patients underwent cataract extraction in both eyes and achieved extremely good vision results. I can recall one patient in particular from the military -- this was a patient who had early nuclear sclerosis preoperatively. He was a -7. We had the discussion about, well, we could do LASIK before your next appointment but then would

have to worry about lens calculations; having the ICL may speed up the cataract development. He opted for ICL, and a year and a half later, he did have cataracts that needed to be operated on. They were explanted, standard cataract surgery was performed, and he maintained uncorrected 20/20 vision in each eye and was still very happy.

DR. CHAMBERLAIN: And how old were the three patients again? I'm sorry.

DR. PARKHURST: So he was in his 50s. One of the patients was subsequently diagnosed actually with lupus and put on systemic prednisone and developed a PSC cataract. He was in his 30s, but I don't think it was related to the ICL. And I had one patient also in her 30s that had an anterior subcapsular cataract due to low vault.

DR. HILMANTEL: Dr. Harton, do you have anything to add?

DR. HARTON: Yes, ma'am. The question of your cost, I think is a good one. I would like to state that we charge about five to six hundred dollars more for an ICL surgery than we do for a LASIK surgery per eye. But what we have to realize is it costs more to do an ICL surgery. The lens implant has a cost to it, and you have to use OR time for it. It's not done usually in your own office like a LASIK is, so I think that's an important part.

With regard to the learning curve, it's also important to know the way ICL surgery has been described, it's phako without the phako. You know, if you're a cataract surgeon and you've done surgery for many, many

years, it's the same. You're just inserting a lens without having to take the first lens out, so it's actually a much easier surgery than a cataract surgery.

DR. HIGGINBOTHAM: Just as a general comment, FDA doesn't deal with costs. It's the CMS, so this is interesting information but not relevant to our deliberations today.

Dr. Huang?

DR. HUANG: Andrew Huang. I'm actually very perplexed by the kind of dichotomy response. One is that, simply, I'm underwhelmed by the results presented by the Sponsor, you know, in that over the course of 10 years, we have about 194 eyes evaluable. And then, you know, that from the community, we have overwhelming response, you know, I mean, there are surgeons who have done, you know, thousands of these surgeries.

So my question is maybe to Dr. Eydelman and maybe to the Sponsor, you know, is there any way, you know, we can, you know, have a retrospective review of those cases that have been done to substantiate the efficacy or even the safety of this device rather than, you know, just base it on the so-called approved protocol?

DR. HIGGINBOTHAM: Is there anyone who would like to respond?

DR. WEISS: I think my assumption is these -- the discussion is about the MICL not the toric, and I think that's where the discrepancy is.

DR. EYDELMAN: This is Dr. Eydelman. Perhaps we can close

the Open Public Hearing before we start questioning back to the FDA and the Sponsor to adhere to the protocol.

DR. HIGGINBOTHAM: Save the question.

There is one question that we have for Dr. Parkhurst if you wouldn't mind coming to the podium. Are you here in any official capacity from the military?

DR. PARKHURST: Thank you for -- Dr. Parkhurst here, and thank you for asking that question. Absolutely not. I do not represent the government, the U.S. military, the U.S. Army in any way whatsoever. These are all my -- strictly my personal opinions.

DR. HIGGINBOTHAM: Thanks for that clarification.

Any other questions to our public? Yes?

DR. CHAMBERLAIN: Just to any of the surgeons who stood up and spoke, we talked a little about measuring vault and sort of paying attention to that in the postop period, and given the level of success that you've commented on, how many of you monitor your vault depth periodically and routinely after your surgeries, and do your vaults tend to fall into those ranges that we've discussed in the study?

DR. HIGGINBOTHAM: Thank you, Dr. Chamberlain, for your question.

DR. DOUGHERTY: Dr. Dougherty here. And I've studied this extensively. It's one of my areas of research interest. I monitor every single

one. And, essentially, we get adequate vault on virtually all of our patients. I haven't seen -- we don't have a lot of problems with vaulting.

DR. CHAMBERLAIN: What is adequate vault?

DR. DOUGHERTY: Okay. Adequate vault, in my opinion, is 100 microns to 1,000 microns. The literature shows that less than 100 microns significantly increases the rate of cataract formation. Greater than 1,000 microns increases the rate of an angle closure.

DR. HIGGINBOTHAM: Thank you.

We have one last question from Dr. Saheb?

DR. SAHEB: For those surgeons who have reasonable experience with the MICLs and were part of the studies or have any experience with the Toric ICLs, can any of you comment on any differences in the surgical implantation, the rotation part of the procedure and the learning curve?

DR. SCHNEIDER: Dr. David Schneider. Having implanted both of these types of lenses, the learning curve is very minimal, but the rotation is a critical part of the Toric ICL procedure. And I've conducted some classes in teaching physicians this procedure. It's important how we determine where we're going to rotate the lens and that the lens be gently rotated, but it's a simple procedure, and it's easily done by any proficient surgeon.

DR. SAHEB: Would it compare to the differences between toric IOLs and monofocal IOLs in the posterior chamber, the skill set? Would you

say that it is similar?

DR. SCHNEIDER: You said something about --

DR. SAHEB: So the differences between implanting a Myopic ICL and a toric ICL, would you say the skill set differences would be parallel to toric intraocular lenses in the capsular bag versus monofocal intraocular lenses?

DR. SCHNEIDER: I would say it's similar, yes.

DR. HIGGINBOTHAM: Great. Thank you.

Yes, Dr. Macsai?

DR. MACSAI-KAPLAN: I just have one more question about the Toric ICL. Maybe Dr. Schneider can come back.

(Laughter.)

DR. MACSAI-KAPLAN: Sorry. Have you implanted any of these using intraoperative interferometry for positioning?

DR. SCHNEIDER: No.

DR. MACSAI-KAPLAN: So I'm curious, were these implanted before intraoperative interferometry existed? I'm not so good on the history part.

DR. SCHNEIDER: I don't feel that I'm qualified to answer that question.

DR. MACSAI-KAPLAN: Okay.

DR. SCHNEIDER: Does anybody else have an answer?

DR. MACSAI-KAPLAN: Okay. Thank you.

DR. PARKHURST: Yeah, it was before that we had -- that was before ORA --

DR. HIGGINBOTHAM: Please approach the podium and state your name.

DR. PARKHURST: Dr. Parkhurst here. The FDA study with the Toric Implantable Collamer Lens took place before widespread use of the ORA devices for intraoperative aberrometry.

DR. HIGGINBOTHAM: Okay. Any other questions from the Panel for the public?

(No response.)

DR. HIGGINBOTHAM: Now we will close the public -- oh, one last thing. Okay. All right. There is a statement that was in the folders of the Panel members that they would like to be read into the record, so thank you, Dr. Weiss, for reminding us of this.

So I have the privilege of doing so, so you can time me for five minutes.

(Laughter.)

DR. HIGGINBOTHAM: This is Dr. Eve Higginbotham. The statement comes from Paula Cofer from Tampa, Florida.

"I appreciate the opportunity to present my concerns to the Ophthalmic Devices Panel regarding the premarket approval application for

the Visian Toric Implantable Collamer Lens.

"My interest in phakic intraocular lenses came about as a result of my disastrous outcome from LASIK eye surgery. Like so many other LASIK patients, I suffer from intractable dry eyes, and my night vision is severely impaired due to my large pupil size. The information I was given about these potential complications during the informed consent process was grossly inadequate. It has been my experience that physicians who perform refractive surgery do not consider these problems as injuries even though they may have a profound negative impact on quality of life.

"Since having LASIK, I have connected with hundreds of other injured refractive surgery patients, and I continue to dialogue with patients on almost a daily basis. Prospective refractive surgery patients often ask me about alternatives to LASIK. My answer is always the same. Keep your glasses.

"Before LASIK, there was radio keratotomy, or RK. Although many renowned eye surgeons touted the benefits of RK, most people today consider RK to be a barbaric surgery. The majority of RK patients are back in glasses, and many are miserable with their vision.

"As problems with RK emerged, photorefractive keratectomy, PRK arrived on the scene. However, PRK carried risk of haze with deep ablations, limiting the pool of candidates. Pain and delayed healing associated with PRK limited its marketability, and complaints of dry eyes,

night vision problems, and regression plagued PRK surgeons.

"Next came LASIK, with its flap and zap appeal, and many ophthalmologists were enticed by the easy money of LASIK. Millions of people with blind faith, myself included, were lured by ads promising a safe, quick, and painless way to eliminate their need for glasses. Once again, it wasn't long before widespread problems began to emerge. Patients who were previously happy with their LASIK outcome were returning with delayed complications, such as corneal ectasia. Problems with LASIK caught the media's attention and stories of LASIK disasters, including LASIK-related suicides, began appearing in print and online. Injured patients contacted the FDA and filed citizen petitions seeking restrictions on LASIK. These events culminated in a 2008 meeting of this very panel, which I served on as Patient Representative, to consider patients' experiences with LASIK. In response, the FDA announced that it would study how LASIK affects quality of life. Six years have passed with no word from the FDA on the results of its LASIK study. During this period, thousands of people have been injured needlessly by LASIK.

"Next down the pike were phakic intraocular lenses, also known as implantable collamer lenses, or ICL. They are more commonly known as implantable contact lenses, a marketing term used to take the fear out of having a dangerous device implanted inside your eye.

"The Visian ICL is placed in the posterior chamber of the eye

behind the iris and in front of the crystalline lens. If the ICL touches the cornea, it will damage the endothelium, which may lead to need for corneal transplant. If the ICL touches the crystalline lens, it will result in cataract formation and need for removal of the ICL subsequently with cataract surgery. ICLs also carry risk of glaucoma, retinal detachment, and other serious complications. Furthermore, patients with large pupils are at risk of night vision problems due to ICL's small optic diameter, consistent with the pattern seen with other forms of refractive surgery. Unfortunately, the applicant did not assess low-light pupil diameter in this study. I urge the Panel to recommend that the FDA require assessment of pupil size for stratification with post-ICL visual symptoms.

"Even more troubling, endothelial cell data were not assessed in this study. As stated, ICLs are associated with endothelial cell loss, which is progressive and may lead to a need for corneal transplant. In the Visian Myopia ICL post-approval study, approximately 6% of eyes with data were noted to have significant endothelial cell loss, that is, greater than 30% from baseline, at four to six years postoperatively. In a five-minute search of the FDA's database of ICL injuries, I located a report of a patient who actually underwent successful ICL implantation who presented eight years later with corneal edema and low endothelial density. It's important to remember that ICLs are marketed to relatively young patients whose endothelial pumps need to last several decades. I urge the Panel to recommend a clear and

strong warning in the labeling regarding endothelial cell loss.

"What do RK, PRK, LASIK, and other lesser known forms of refractive surgery have in common with ICLs? They are all medically unnecessary. This bears repeating. ICLs and other forms of refractive surgery are unnecessary. History has shown that once an ophthalmic device receives approval and goes to market, the FDA is unlikely to intervene when problems emerge. In the context of a medically unnecessary surgery that carries risk to a very necessary organ of the body, the risk tolerance should be near zero. Members of the Panel, in light of significant safety concerns raised in the Visian TICL study, I ask that you cast your vote against approval.

"Thank you for your consideration."

And, again, that was Paula Cofer from Tampa, Florida.

Now the Open Public Hearing is closed.

There will be some time for the FDA at this point to present some additional information.

DR. EYDELMAN: Thank you. My team, please approach the podium.

Madam Chair, we tried to make couple of slides to address the questions that remain from the morning, and just give us a minute to load them up.

DR. HIGGINBOTHAM: Thank you, Dr. Eydelman. About how much time do you project?

DR. EYDELMAN: However long it takes to locate the plug.

(Laughter.)

DR. HIGGINBOTHAM: Understood.

(Pause.)

DR. HIGGINBOTHAM: Are you ready?

DR. EYDELMAN: Yes.

DR. HIGGINBOTHAM: Yes?

Please state your name.

DR. HILMANTEL: I'm Gene Hilmantel. Prior to the break, there were some questions about confusion in the rotational data. I apologize for the confusion, but there's a lot of data here.

So there was a question about, in this slide here, the percent of eyes that were -- you see in that row about the less than 30-degree misalignment. It goes from 100% at three months, 100% at six months, and then 99% at greater than or equal to 12 months. So the question was did an eye rotate a large amount in that period. So the answer to that is no. There was a single eye that had a 78-degree misalignment at the one-day visit, and then that eye had the same misalignment at the one-week visit. And then there was missing data until the final visit at greater than or equal to 12 months. And at that visit, the guy again had 78-degree rotation, so it didn't rotate in that time span, but there was missing data. And, again, this just kind of sort of illustrates maybe some confusion and difficulties that we have

created by a lot of missing data in this study.

DR. HIGGINBOTHAM: Just to clarify, you said 78 degrees?

DR. HILMANTEL: That's correct.

DR. HIGGINBOTHAM: Thank you.

DR. HILMANTEL: Yes. There were a number of eyes that had very large misalignments at the time of surgery, or Day 1. I believe it was about on the order of 15 eyes. And so some of them were clearly surgeon error. And others, there was sort of no explanation. Sometimes the surgeon got confused. There were a couple cases where, clearly, they rotated the major axis of the lens to the target orientation for the axis, and they got confused.

DR. HIGGINBOTHAM: Dr. Saheb, I think this was your question. Do you have a follow-up, or are you satisfied?

DR. SAHEB: You just said a large number were grossly rotated, and here we see that at one year, only one patient was, so does that mean the rest of those that you said were largely rotated were fixed in the early postoperative time? You said about -- I think you said 14 or so. So if we're down to one at one year, were those fixed early on, or did they become missing?

DR. HILMANTEL: No. There were two surgeries that partially or fully corrected rotational error. A fair number of the eyes kind of disappeared, and my computer just died, so I don't --

(Laughter.)

DR. EYDELMAN: Well, then, we'll proceed to the next, and then perhaps we can come back --

DR. HIGGINBOTHAM: Excuse me, Dr. Chappell, do you have a quick question?

DR. CHAPPELL: Just a quick comment. For those who are interested in the distribution of that, that's in figure 5 in the Executive Summary if you wanted to take a look.

DR. HIGGINBOTHAM: This is Dr. Higginbotham. Is figure 5 able -- can we project that --

DR. CHAPPELL: Page 131.

DR. HIGGINBOTHAM: -- so everyone can see the same thing that we're seeing? Is figure 5 a slide? We just want to make sure that everyone can see the same thing even beyond the Panel, so --

DR. CHAPPELL: Can you plug a laptop -- can you plug it back into the projector easily?

UNIDENTIFIED SPEAKER: Which figure 5? Are you talking about in the Executive Summary?

DR. CHAPPELL: Yes. It's called Assessment of Absolute Angle of Rotation by Fixation Angle and TICL Rotation. And it shows exactly what he's saying, is that this huge 78-degree rotation and then a scattering of ones around 20, and then the rest way far -- oh, yeah, sorry.

DR. HIGGINBOTHAM: Can someone from the FDA walk us through this figure since it's been brought to our attention generally? And may not be quite as visible in the back of the room.

DR. HILMANTEL: Gene Hilmantel. Okay. So this is a figure that the Sponsor created in response to our questioning them about the effect of fixation angle on the postoperative rotation. I need to take a closer look.

DR. HIGGINBOTHAM: Would you like a moment, and then we can come back to this point?

DR. HILMANTEL: No, that's fine. I can see it now.

DR. HIGGINBOTHAM: Okay.

DR. HILMANTEL: Okay. So the y-axis is the postoperative angle of rotation, and the x-axis is the fixation angle. And so the Sponsor put in various -- a couple of different kind of fits. I think the -- I believe the blue line there was a straight line regression fit, and the red line, I believe, was some sort of spline with a couple different curvatures. And that dotted red line was some sort of confidence interval on that redline fit.

So what this is basically showing is that there's only -- I don't know what I did there --

(Laughter.)

DR. HILMANTEL: We're green here. But this is just showing that there's only a weak relationship between the postoperative rotation and the fixation angle. That was the point of this figure.

DR. CHAPPELL: This is Rick Chappell. That's true, but it coincidentally, conveniently gives the distribution.

DR. HILMANTEL: Yes, you're absolutely right. I'm sorry. That's absolutely correct.

DR. EYDELMAN: Okay. Thank you. Perhaps we can move on to the next set of slides.

DR. HIGGINBOTHAM: Dr. Macsai, you have a question about this graph?

DR. MACSAI-KAPLAN: Yeah. I have a follow-up question. When you look at this graph, and maybe I just need some education, there's a whole bunch of dots at 20 degrees absolute angle of rotation. So does this mean that the Toric ICLs are put in, and they're 20 degrees off? Or does this mean they're put in, and they have to be rotated 20 degrees to be in position where they get their ultimate astigmatic effect? Because I understood it to be the second one.

DR. HILMANTEL: Are you talking about the x-axis or the y-axis? I'm sorry.

UNIDENTIFIED SPEAKER: Talking about the y.

DR. EYDELMAN: The y-axis.

DR. HILMANTEL: Okay. So --

DR. MACSAI-KAPLAN: So what I'm asking you is, is this how far you put the ICL in at 180 or 0, and then you have to rotate it 20 degrees to

get it into the position for the ultimate effect, or are you saying these are 20 degrees off of where you intended them to be? Do you understand the question?

DR. HILMANTEL: Yeah, it's neither of those. The y-axis is the angle of rotation postoperatively, how much the lens has rotated after implantation over the course of the study.

DR. HIGGINBOTHAM: Let me just remind the Panel, there will be the opportunity to ask questions of the Sponsor. We just can't ask them at the same time. So if you'd like, you could save this. Okay.

DR. HILMANTEL: So, again, the x-axis is the fixation angle. That's the amount of surgical rotation that the surgeon has to rotate the lens to get the axis in the correct position.

DR. CHAMBERLAIN: So I'm not understanding that. It sounds to me like what you're saying is, is that the y-axis is the amount it's off after surgery. The surgeon rotated it into the correct position, but the absolute angle observed after surgery in some of these points is now up to 20 degrees off. Can you clarify?

DR. HILMANTEL: No, I'm sorry. The y-axis is just how much did the lens rotate from the time of surgery through the course of the study. That was just the observed rotation.

DR. CHAMBERLAIN: So isn't that what we're saying, that it's off from the intended location, from the intended position? Are you implying

something different?

DR. HILMANTEL: No, that's not necessarily true.

DR. MOKHTARZADEH: It depends whether the surgeon -- this is Maryam Mokhtarzadeh. One thing it depends on is whether at the time of surgery it was put in at the exactly correct axis. So that's why we refer to it as absolute angle of rotation. We want to know whether the lens remains stable or not. This isn't assessing whether it's -- how far off it ended up from the desired angle. Does that make sense now?

DR. HIGGINBOTHAM: And this is the last available visit.

Yes, Dr. Glasser?

DR. GLASSER: David Glasser. So one last bit of information. At what time point are all these? Is this at the last visit? Is this at 12 months?

DR. HILMANTEL: This is Gene Hilmantel. This is at the last available visit.

DR. WEISS: Jayne Weiss. So what percentage -- how many degrees do we expect the average lens to rotate at the last visit?

(Laughter.)

DR. WEISS: I'm always good for a laugh.

DR. EYDELMAN: Perhaps that question is better addressed to the Sponsor, how much they -- I guess we can only answer what's written in the protocol. What we hope for is kind of a question for the Sponsor.

DR. WEISS: Okay.

DR. HILMANTEL: Okay. So maybe this slide will clarify things. Okay. So, again, just to reiterate, there were two different ways that the Sponsor assessed the actual misalignment from the intended position through the direct measurement at slit lamp and through the calculation, vector calculation based upon the manifest refraction. And can you go to the next slide? Let's skip that.

Okay. So this is from the direct measurement, so that final column shows the distribution of misalignment from the intended position based on the direct measurement.

And then if you go to the next slide, this is through the other method of assessment. This is from the manifest refraction, and this gives the same kind of information, the distribution of the misalignment from the intended position based on this error of angle analysis.

DR. EYDELMAN: Gene, perhaps you want to address the difference of capturing the data between the two presentations.

DR. HILMANTEL: Yeah. Okay. So looking at these two slides, you'll see that the *n*'s are quite different between this slide and the prior one, and that's because there's a lot more missing -- this direct measurement was often not done by the investigators even though the patient was there at the visit. They, in most cases, did the manifest, though there were a few cases in which that was missing as well. So there's more data available for the manifest.

DR. HIGGINBOTHAM: Thank you. Are there any other points you'd like to highlight, FDA?

DR. EYDELMAN: Yes, hold on.

Gene?

DR. HILMANTEL: Excuse me. I didn't hear the question. I'm sorry.

DR. HIGGINBOTHAM: Proceed.

DR. HILMANTEL: Okay. So Tieuvi, if you can go back to the one before this. Okay. So there may have been some confusion from this slide earlier in the presentation, and this -- that line there that says analysis of 13 eyes of greater than 15 degrees rotation between visits, that was based upon an early submission that the Sponsor made, and some of that data kind of disappeared later on after the audit. But this first raised our concern about the methodology of the rotational method because the Sponsor was saying this direct observation method was often in error and appeared be a very inexact assessment. But this does not represent the final data.

DR. HIGGINBOTHAM: This is Eve Higginbotham. A clarifying question. Do you know if the 13 eyes received one of the 80 potential toric lenses that were being made off the record or was it one of the standard degrees of --

DR. HILMANTEL: I don't know that. That's probably not that relevant, actually, because this just had to do with the observations of the

lens orientation.

DR. ZABRANSKY: Question. Related to that, we have seven surgical -- or seven study sites. Were these misalignment situations occurring at any one particular site more frequently or with any one particular surgeon? These appear to be outliers, to some degree.

DR. HIGGINBOTHAM: Thank you, Dr. Zabransky, for your question.

Do you have an answer, FDA?

DR. HILMANTEL: I don't have an answer at my fingertips, no.

DR. ZABRANSKY: Perhaps the Sponsor will.

DR. HIGGINBOTHAM: Hold that thought.

Any other comments from FDA?

DR. EYDELMAN: Yes, I -- oh, go ahead.

DR. HILMANTEL: Yeah, I wanted to address one of the prior questions about the issue of whether the problem was with the protocol or with the study conduct, what seemed to be sort of how could we attribute the problem. So at FDA, we see sort of a wide variety of protocols submitted in the IDE phase, in terms of what is actually -- how much detail there is in the protocol. This protocol was, in some ways, similar to a LASIK-type protocol, refractive surgery protocol, and I've seen a large number of those submissions. And some sponsors give a great deal of detail spelled out in the protocol as to their standard operating procedures for how they'll do things

like manifest refraction and various procedures in the study. Other sponsors give very little detail. We don't really insist on a lot of detail for some of these procedures, and we kind of, to some extent, leave it up to the sponsor to run a study that will develop quality data.

Now, in this case, it turned out there were, unfortunately, a number of problems. I mean, for example, the sponsors will often have extensive training for their investigators, in terms of how they want the procedures run during the course of the study. And in this case, we investigated and we found that the Sponsor didn't have sort of any standardized training whatsoever for their investigators.

DR. EYDELMAN: Does that address your earlier question, Dr. Weiss?

DR. WEISS: I think that's incredibly helpful because it puts most of the burden on the Sponsor for a poorly executed study, which gives us as Panel members very confusing data, which makes it much harder to assess. And that is the burden, then, and that's the responsibility of the Sponsor, from what you're saying, to have the compulsiveness to put the data points in there, to make the study easy to interpret, and so that if the results are good, to make those results clear. In this case, from what you've said, every single eye had some deviation, which is a poorly done study. Thank you, though, for letting us know that.

DR. MOKHTARZADEH: Okay. Just to follow up on something

else, an issue that was raised this morning, there were some questions asked about pigment-related topics, transillumination, otherwise. I just want to review a couple things quickly to give you a little more information. With regard to transillumination defects, again, as we said, these weren't specifically assessed under the TICL study. In the MICL study, it was looked at, and 9.89%, that is, 52 out of 526 eyes did show transillumination defects. Next slide. Thank you.

In the TICL study, one set of data we have that could be somewhat compared to the MICL study is pigment deposition on the ICL. So in the MICL study, this was noted in 8.37% of eyes, that 44 out of 526 eyes. In the TICL study, pigment deposition on the ICL was intended to be -- it was listed in the protocol as a complication. Therefore, there was some data recorded on this. Now, I believe the number from the MICL -- again, it's the post-approval study we're looking at here -- but it addresses cumulative occurrence. So if you look at the table -- and I apologize for the small font; it was difficult to extract this data in the time given -- you can see that, for example -- oh, you know what? The table is referring to pressures rather than the pigment deposition. Yeah, it's the wrong table on there.

What I can tell you -- I apologize for that -- what we saw in the study was that a similar table was provided to us showing us the pigment deposition at various time points. Now, at the 12-month visit, what I recall off hand -- it's actually table number 34, I believe.

DR. EYDELMAN: We're going to pull it up in a second.

DR. MOKHTARZADEH: Tieuvi will pick it up --

DR. EYDELMAN: It was just in the haste during lunch, a wrong table got inserted, so just bear with us for a second.

DR. MOKHTARZADEH: That's going to come up later. I think it was table 34 or 35 in the FDA Executive Summary, Tieuvi, if I remember correctly. Yeah, pigment deposits. Thank you. So when you look at that, you can look at the numbers and see that at one day postoperatively, you see one patient there listed with trace or light. At one week, it says -- I'm sorry. I'm saying patient. It could be -- it's eyes, actually, because it's 210. So you can see it looks like four patients at one week were noted to have something, at one month, 1 plus 9 plus 7 plus 1. So you go through and you kind of get a sense of how often this was occurring in the TICL study.

The reason I couldn't provide you a formal analysis for this is because, again, I can't tell you how many of these are occurring in the same eye, for example. This wasn't data that was presented to us in a way that I could give you an apples-to-apples comparison with what we saw in the MICL study. But, again, there was some information related to pigment, in this case, pigment deposition on the ICL, that was given to us during the TICL study. So you do see that there is some occurrence of that.

If we can go back to the slides now? Next --

DR. HIGGINBOTHAM: Can we ask a question, a brief question?

DR. MOKHTARZADEH: Absolutely.

DR. HIGGINBOTHAM: So do we know if there was -- this is Eve Higginbotham -- any standard method for actually assessing pigment related to standard photographs?

DR. MOKHTARZADEH: So these were slit lamp observations. And, again, as I mentioned, where it was listed in the protocol was simply as a complication, meaning something that we wanted to know about. That said -- so can you go back to the other slide? If you can't, it's fine. In that table, again, it is in the Executive Summary, if you see that second to last row, it says not specified. So there is a number of patients at each time point you can see, like at 12 months it's 53, where it's not specified. And, again, it was intended to be recorded as a complication.

DR. EYDELMAN: And, again, just to -- this is Malvina Eydelman again. Just to reiterate Gene's point earlier, for something like this, we would expect the Sponsor to have an SOP for capturing, and we might defer to them.

DR. MOKHTARZADEH: Okay. And then, to follow up again, I believe this is the second to last slide. But on pigment-related topics, abnormal pigment in the angle in the MICL study, this is giving you a little more detail about what happened since, again, that is where the major body of information we have on pigmentary issues with this ICL lens platform comes from. What we saw was between four years postoperatively and five

years postoperatively, there was an increase. So this did appear to be something -- at four years postoperatively, as you see on the slide, it was 0.8%, that is, 4 out of 248 eyes. At five years postoperatively, it was approximately 4.8%, 16 out of 335 eyes.

And kind of I don't want to say in contrast, but on the other side, if you look at transillumination defect in that same study, you see a lot of those cases immediately postoperatively. For example, it says 23 at one day postop; one month to one year, you see 15; two to three years, 11; four to five years, 5. So, again, the thing that we're trying to give you a sense of is the timing of when these occurrences were kind of picked up on. And this, again, is data from the MICL PAS study.

I do want to note that I believe that gonioscopy in the MICL study was not -- Gene, correct me if I'm wrong -- but was not part of the original protocol. It was something that was asked to be collected at the four- and five-year data. That's why I'm presenting that.

DR. HIGGINBOTHAM: Yes, there's a question.

Dr. Weiss?

DR. WEISS: I've never seen transillumination defects go away, so if the Sponsor knows how to do that, I'd like them to tell me after this is all done.

(Laughter.)

DR. WEISS: So I think that just shows the data is not -- it should

be -- it may not be accurate, because transillumination defects don't go away.

DR. HIGGINBOTHAM: Yes, Dr. Jeng?

DR. JENG: In follow-up to that, I think it's also important for us to know if there's any way whether these are transillumination defects from trauma from surgery or if they're chronic occurring because they're rubbing on the lens itself, and so the positioning of it would be helpful to know.

DR. MOKHTARZADEH: I'm sorry. This is Maryam Mokhtarzadeh. I missed the question.

DR. JENG: So the pattern of transillumination defects can actually tell us a lot.

DR. MOKHTARZADEH: Um-hum.

DR. JENG: And so we should be able to tell whether the pattern is from trauma from insertion of the lens at the time of surgery or if it's a chronic thing that is from chafing and rubbing on the iris.

DR. MOKHTARZADEH: That's an interesting point.

DR. JENG: But either way, Jayne is right. Transillumination defects don't go away.

DR. MOKHTARZADEH: Right. And I wanted to address that. I believe that these were new occurrences. I don't think this was a -- this wasn't saying that there were 23 patients at one-day postop and 5 at four to five years. I think we were trying not to double account, if I interpreted the data correctly.

DR. WEISS: This is Jayne Weiss again. Then Dr. Jeng's comment becomes even more important.

DR. MOKHTARZADEH: Um-hum.

DR. WEISS: Because you should not be getting this four years new ones and five years new ones.

DR. MOKHTARZADEH: And I think it's a very good point that the pattern could be appropriate. I don't think that is data that we have at this point, to my knowledge. It isn't anywhere that I've seen. But I think that's a very good point to keep in mind.

And, again, just generally, I want to thank the Panel for all the thoughtful comments, both about the adverse events and the protocol deviations. Definitely you guys are catching a lot of serious issues that we want your input on.

Thank you.

DR. EYDELMAN: I have one more point from this morning to address.

DR. HIGGINBOTHAM: Thank you, Dr. Eydelman.

DR. AHN: My name is Chul Ahn. I am a statistician. It is about applicant's sensitivity analysis, and I noticed that several Panel member had a question about it. So I traded my lunch to make one slide about it.

(Laughter.)

DR. AHN: So this is what I came up with. The applicant

presented the sensitivity analysis to show that protocol deviations and out-of-window visits do not affect study outcomes. However, these analyses have some drawbacks. This is, essentially, the subgroup analysis to compare clinical outcomes between subgroups with and without protocol deviations. The p-values in this analysis ranges between 7% and 94%. You might say that these p-value greater than 5% indicate that there is no difference in clinical outcome between subgroups. But this is exactly the dilemma with the subgroup analysis.

The clinical study is usually sized for the overall treatment effect and very rarely for the subgroup, and this was not sized for the subgroup. So there's insufficient power to detect any significant difference. And the small increase in the sample size for the subgroup may decrease the p-value less than .05.

DR. HIGGINBOTHAM: Thank you very much for that comment. I did fail to recognize Dr. Saheb, who had a question related to the last discussion. Then we'll come back to this point.

DR. SAHEB: It was a comment about the pigment dispersion. Now, pigment dispersion will either occur because of surgical trauma or because of progressive iris chafing, and there were two comments about transillumination defects going away or never going away. And there's some evidence to suggest that in patients with pigment dispersion syndrome, that over time, they can disappear if the stimulus for iris chafing goes away. And

so, here, surgical trauma would be different than pigment dispersion syndrome related to iris chafing, but I'm not sure we could be so absolute about them never going away. There is some evidence to suggest in pigment dispersion they might.

DR. HIGGINBOTHAM: Thank you for that comment.

Any comments from the Panel about the last comment about sensitivity analysis, or question, I should say, clarifying question?

(No response.)

DR. HIGGINBOTHAM: Seeing no hands, Dr. Eydelman, is that the completion of -- Gene, yes?

DR. HILMANTEL: I'm sorry. Gene Hilmantel, FDA. I just wanted to try and clear up an earlier question that I wasn't able to answer. So what I'm looking at right now, at the time of surgery --

DR. EYDELMAN: I'm sorry. Is there a table you want us to pull up?

DR. HILMANTEL: No, no, I'm sorry. The day of surgery, there were nine eyes with misalignment from the intended position, nine eyes with greater than or equal to 15-degree error in the alignment position. And at the final visit, there were 11. And I believe one of those nine was surgically corrected to a smaller amount. So the others came on due to rotation after the surgery.

DR. HIGGINBOTHAM: So that would suggest that there was an

additional one that rotated later? Well, there were nine --

DR. HILMANTEL: Well, there were nine --

DR. HIGGINBOTHAM: And then -- yeah, an additional three --

DR. HILMANTEL: -- one was corrected, and so, then, I guess there were probably three --

DR. HIGGINBOTHAM: Yes, an additional three.

DR. HILMANTEL: So, again, that's greater than or equal to 15 degrees.

DR. HIGGINBOTHAM: Yes. Thank you.

Any other questions, comments, points of clarification that are needed?

Dr. Macsai?

DR. MACSAI-KAPLAN: It's not an FDA question.

DR. HIGGINBOTHAM: Okay. Thank you.

Dr. Chamberlain?

DR. CHAMBERLAIN: Yeah, this may be just sort of a general question. Does the FDA -- and if they presented this, I apologize for missing it -- some sort of a sense about variability of -- was the study able to assess the variability of the surgeon component. And I guess what I'm getting at here is it seems like there is arguments about surgically induced astigmatism in the incisions that are made. There may be arguments about whether there's an outlier effect at one particular site, where we saw more perhaps pigment

dispersion or other types of side effects. So if this is released to the public, would the average surgeon experience what the surgical test sites experienced, or is there some sort of an effect here that these are exceptional surgeons and we didn't have a large enough variability sampling to know that? So I don't know if that makes sense.

DR. HILMANTEL: Yeah, I think it's the latter case, that we really don't have a large enough sample. These things occurred at a fairly low percentage. So when you're talking about on the order of 200 eyes, and you're losing a few people along the way, it's hard to develop any statistically significant assessment of differences there.

DR. HIGGINBOTHAM: All right. Any -- okay, so we have Dr. Macsai, then Dr. Huang.

DR. MACSAI-KAPLAN: Dr. Macsai. And I'm not sure if you have data that answers this question, but if there is rotation, is there associated zonule damage? Did you have any evidence of that?

DR. HILMANTEL: Yeah, I don't believe we had any reported zonular damage.

DR. EYDELMAN: This is Dr. Eydelman. I suggest you ask the same question of the Sponsor, however.

DR. HIGGINBOTHAM: Any other questions? Yes. Oh, Dr. Saheb -- oh, Dr. Huang and then Dr. Saheb.

DR. HUANG: I want to just thank FDA for that very thorough

analysis, but I have question, you know. Given there were some protocol deviation, but if the data, as thin as it is now, the information enough to justify the endpoint, did they meet all the criteria FDA set out for them to meet, you know, such as, you know, the safety guideline and such as the refractive outcome?

DR. EYDELMAN: Dr. Eydelman, Dr. Huang, we're looking forward to yours and other Panelists' comment on that exact point.

DR. HUANG: I can see the results by myself, but I wasn't sure if that --

DR. EYDELMAN: We're looking for you to share your thoughts with us.

DR. HUANG: -- the results, and I mean, the number as that -- the last statistical analysis say, you know, it's underpowered. But based on the information we have, is the -- those data presented, you know, in terms of meeting the endpoint, if it's sufficient to draw a conclusion. That part, I'm not very clear.

UNIDENTIFIED SPEAKER: I think the primary endpoint was met in the current analysis, but because of a lot of missing data, we don't know how -- depending on how these missing data are imputed, the result may change.

DR. HIGGINBOTHAM: Dr. Saheb, you had a question?

DR. SAHEB: This question is for Dr. Eydelman. Just some

guidance as to what you'd like us to focus on. Are we looking today at the safety and effectiveness information of the Toric ICL in comparison to the already-approved ICL or are we reevaluating ICLs in the context of this application?

DR. EYDELMAN: So each PMA stands on its own. We're here today to try to determine safety and effectiveness of TICL, which is the subject of this PMA. And with that, we're looking to your very thoughtful discussion to come of our specific questions to this regard.

DR. SAHEB: Thank you.

DR. HIGGINBOTHAM: Okay. I think that -- okay, Dr. Weiss?

(Laughter.)

DR. WEISS: A follow-up for Dr. Eydelman. Our discussion should be based on history and things aside from the study of the Sponsor, or it should be based on the Sponsor's study?

DR. EYDELMAN: Your discussion should be on all the knowledge currently available, and that's why we were hoping we were very prescriptive and precise in our presentation to show where each source of data came from.

DR. HIGGINBOTHAM: Okay. Seeing no other hands or body language suggesting that there is a question, I'd like to thank the FDA for this extraordinary presentation and additional clarification of some of the points that we questioned earlier.

At this point, I think it will flow better, and I'm looking across the Panel that we may take a break now and then start our Panel Deliberations after the break, with the Sponsor coming to the -- and I can see Sponsor likes that plan, too, so that everyone has at least a chance to catch their breath, because this is the last break of the day, but we will end at 6. So it's going to be back and forth between Sponsor and FDA in terms of coming to the table. So we will reconvene at -- we'll just reconvene at 3:15.

(Off the record.)

(On the record.)

DR. HIGGINBOTHAM: I now have 3:15, and I see all Panel members assembled. So now we will begin our Panel Deliberations. Before having Sponsor come to the table, I was going to ask the Panel if they'd like to have an internal Panel Deliberation moment, if you will.

This is also a reminder. This portion is open to public observers. However, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons, and that's including our Panelists, who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

So if we could take maybe five minutes, and is there anyone on the Panel that needs some further clarification or has some burning questions and wants to get some feedback? We have cornea specialists, and we have statisticians and epidemiologist, and glaucoma specialists represented, as

well as our Patient Representative and Consumer and Industry Representative. So any questions or comments?

Dr. Weiss?

(Laughter.)

DR. WEISS: I want you all to observe a rare moment. I'm going to be quiet.

DR. HIGGINBOTHAM: All right. Ms. Schwartzott, do you want to offer some comments about what you've heard so far?

MS. SCHWARTZOTT: Hi, I'm Jennifer Schwartzott. I have a lot of concerns about the -- what has been going on with the study process. But also, as a patient and somebody who has had a toric lens, although it's different from this one, it is a life-changing experience. I went from not being able to drive, not being able to watch TV properly, not being able to, you know, live a full life to getting all those things back. And it's gone from when I was a child till now. So to me, somebody made the question a while back if you ask people if it was worth the risk, to me, it is. It is worth every single one of those risks we've been talking about. To me. And that's my personal opinion.

I had several doctors tell me do not do any of these things. And they said they'd rather have me blind than dead. That's actually what a doctor said. And I took the risk anyway. And I'm benefiting from it. And if the outcome had been worse, it was a risk I was going to take. So I think

that's important to -- I'm not doing it for cosmetic reasons. I'm going to need the glasses the rest of my life for prisms. I was doing it because I was 2400 vision, and I am now 20/25, and we're going to be doing the other eye, and I expect the same results.

So maybe there should be a restriction on who gets this. I don't know. If it's just for cosmetic reasons, maybe it's not worth it. But for a person like me, I took the risk.

DR. HIGGINBOTHAM: Thank you for that comment.

Ms. Latimer, do you have a comment or a question? Either.

MS. LATIMER: Hello, I'm Jody Latimer. As a nurse, I get a lot of questions just from patients asking, gosh, you know, different cataracts and so forth, what could happen. People are fearful. And listening today, it seems as though there is a lack of evidence. There's some missing data. But my question is with the TICL, I was kind of confused with the last question prior to break. The TICL, it rests on the footplates which changes potentially the curvature, which then increases the lens vault, which -- is that what increases the risk of a cataract or increased ocular pressure or retinal detachment of how the TICL rests on the footplates? I was confused with that.

DR. HIGGINBOTHAM: Okay. Does anyone on our Panel like to offer an explanation, and perhaps when Sponsor comes to the table, they could also provide some graphic information to be able to illustrate that.

Dr. Macsai, you'd like to make a stab at that?

DR. MACSAI-KAPLAN: Yeah, I'll take a stab at it, Jody. The vault of the ICL is the clearance of the ICL over the anterior lens capsule, and if the lens rests on the anterior lens capsule, theoretically, it could induce a cataract. If the vault is too high, theoretically, it would increase a likelihood of glaucoma from narrowing of the angle. The footplates, the resting, the position has nothing to do with the retinal detachment. That's just that myopes are at a greater risk for that in my interpretation.

The only thing about this vault that I would add that's a little bit confusing is if there's too great of a vault, I think, theoretically, from an optics perspective, you could create -- you know, the patient would still be myopic, you wouldn't fix the problem, in addition to maybe potentiating glaucoma.

MS. LATIMER: Thank you.

DR. HIGGINBOTHAM: And hopefully we can get a picture for you because I think a picture is worth a thousand words, and I think it'll be a little bit clearer.

Mr. Pfleger, do you have any comments?

MR. PFLEGER: Yes. I think we're in one of those situations where we have a company that started some trials, and then new people came in and they're doing the best that they can to clean up and get the best data that's available to them, recognizing you can't go back in history and

generate data that wasn't collected originally. So if we look at it from the perspective of they've had an independent group go out and look at the data, then I think a lot of the questions I originally had based on going through the review was, all right, this is the data, and we should be able to at least trust that level of data, which doesn't change the fact that there's, you know, some missing, and they're going the best they can to fill it in. So from that perspective, you know, a lot of questions, I think, were resolved that perhaps were as a result of their discussions with FDA and ongoing dialogue with them, so --

DR. HIGGINBOTHAM: That's very helpful.

Dr. Coleman?

DR. COLEMAN: I had a question for Dr. Chappell regarding -- I'm allowed to ask him a question?

DR. HIGGINBOTHAM: Yes, this is internal to the Panel before we invite Sponsor back --

(Laughter.)

DR. COLEMAN: Sorry, put you off guard here. But my question is, is as a biostatistician, your thoughts about the quantity of missing data and -- as a biostatistician, in terms of looking at the statistics and the analyses.

DR. CHAPPELL: Some kinds of errors don't seem severe to me. For example, the mis-timing, the visits that are before or after. As long as

they take place, it doesn't matter much to me especially since this doesn't -- there doesn't seem to be that much change. When there are missing data, I always -- permanently missing data, you don't recapture them later. I always worry about some kind of selection bias, because maybe they had an unsatisfactory result and they said they weren't going to go back to that same doctor, they'll go somewhere else to salvage it. And so never having had a clinical practice, I don't know what the likelihood of that is. It all depends on why they are missing. Ordinarily, I'd say, well, if you're hit by a bus, then that's random. Of course, in this case, it may not be, due to vision, right?

(Laughter.)

DR. CHAPPELL: If they had -- if they died of an intercurrent disease which was clearly unrelated, then I wouldn't care from a scientific perspective. But that's a subjective answer. It's the only kind of answer I could give.

DR. COLEMAN: Thank you.

DR. CHAPPELL: Sure.

DR. HIGGINBOTHAM: Okay. Any other discussion?

(No response.)

DR. HIGGINBOTHAM: All right. We have a little bit of time to make up, so we will invite the Sponsor back to the table. So, Panel, this is your chance to, first, ask the Sponsor any specific questions you may have.

We would like to give the Sponsor at least 30 minutes to do what they would like in addition to responding to our questions, and then we can certainly have a chance to have additional dialogue among us, and then if there are additional questions for the FDA, we can invite the FDA back, but then we'll have to bring the Sponsor back as well after that. So we may be going back and forth a little bit, and a few people in the room are going to get some exercise. But I just wanted to give you a preview of what's to come in the next hour.

Sponsor, you have the floor.

MR. HUGHES: Dr. Schallhorn?

DR. SCHALLHORN: Thank you. Dr. Schallhorn. We would like to address many of the things that were discussed previously. I think starting out really has to do with the discussions about the data, the integrity of the data, whether you can trust the outcomes. And I appreciate that is a major concern of yours. And so I'd like to address that right now in several different ways.

The first is just the strength of the data. The data itself, the outcomes of the data, you saw them. You saw how powerful the data was as far as the ability of the Toric ICL to correct myopia and astigmatism. It can do that with an incredible level of effectiveness. It does that in a safe manner. And so that's the first point to keep in mind is that no matter how you cut the data, you always come back to how strong the data is as far as outcomes go.

Another element here has to do with the audit that was mentioned. A 100% audit of the data was conducted, and that cleared that data. It cleared the data. It was all audited. That means it has integrity. We can trust it. We can trust it to look at and evaluate the safety and effectiveness, which is a very important aspect of it.

Another element has to do with looking at the totality of the ICL platform, the totality meaning look at the Myopic ICL results, which was a larger study. That study also showed that the ICL as a platform can safely and effectively reduce myopia.

And, last, the other peer-review articles. Almost every other peer-review article that's been published has shown the ICL as a platform to be safe and effective. So, in totality, you can see what we're talking about here.

Now, looking at some of the specific issues in the protocol, yeah, I mentioned that the study could have been conducted better. It could have definitely been conducted better. This is a study that was conducted years ago. And so there are really a couple different issues in that regard. One are the protocol deviations. Now, I told you about the protocol deviations. There were many of them. And from a purely study conduct regard, I can understand your concern, because there were many protocol deviations. However, if you drill into what were those protocol deviations, you would realize, certainly, as clinicians and surgeons that most of these

protocol deviations were non-issues, right?

If a toric lens has multiple axes, it's completely transparent to the surgeon. The surgeon just takes lens A and puts it in the eye and rotates that lens. So whether it is made with multiple axes or not does not matter surgically. Likewise if the case report form was not well designed and the data is missing in that regard, that data is still recorded and good patient care is still being conducted. Or lens power out-of-range. Listen, from my perspective, it was a flaw in the protocol. The protocol specified +150 diopters. But surgeons didn't want to put in a +150 lens in a patient with 1 diopter of cylinder. They chose to put in the 1 diopter lens, which was appropriate for the 1 diopter of manifest cylinder that the patients had. So the protocol, the crafting of the protocol, the writing of the protocol was in error. But that shouldn't stop us from looking at the data, the outcomes that the study had.

And so, you know, the protocol deviations are one aspect. And we talked about sensitivity analysis and the sensitivity that we've conducted. So I'd like to ask the biostatistician, Dr. Smits, to come up and describe the methodology of conducting these sensitivity analyses.

Could we have the slide?

DR. SMITS: Hi, my name's Gerard Smits. I'm a statistical consultant, paid consultant to STAAR Surgical. I've been working in this area for about 25 years, currently consult to a number of vision-related companies

such as B&L, HOYA, Refocus, ReVision Optics, Presbia, and AccuFocus. I'm also a statistical reviewer for BIS, the notified body in Great Britain.

If we look at this, here's an example of some of the sensitivity -- the sensitivity analysis we did on MRSE. The top box shows the point estimate with 95% confidence interval for all available eyes. The modeling was done -- the modeling I used here was a general estimating equation models that would account for about two-thirds of the subjects had paired data eyes, so these confidence intervals should be reasonably accurate. I was using a identity link function, which is very similar to running a linear model.

Anyway, you can see that the point estimate shows that the mean MRSE is just a hair greater than 1, and this estimate will vary a little bit from the numbers you've seen before, because the numbers you have seen before are equally weighted by eye. This takes into consideration the dependence in the data, so the point estimates can be a little bit different. Anyway, so you can see the mean MRSE is slightly greater than positive with a fairly tight confidence interval, which spans 0.

Now, one of the -- we have a number of ways of breaking down the data, and we had to kind of pick and choose. We tried to pick the categories that might be of interest to people. And one area that seemed to be important was before the window, in the window, after the window for the 12-month visit. And so that was one of the approaches we used for cutting the data. Another was whether there was a major protocol deviation

or not.

Now, there's been some discussion earlier about whether STAAR Surgical's definition of major was the best way of doing it; there may be others. However, I was able to --

DR. HIGGINBOTHAM: Excuse me. I'm sorry for the interruption. Dr. Eydelman would like to make a comment.

DR. SMITS: Oh, I'm sorry.

DR. HIGGINBOTHAM: Sorry about that.

DR. EYDELMAN: I'm sorry to interject, but per our previous conversation, prior to presenting any data that wasn't submitted to the FDA, please state that prior to its discussion.

DR. SMITS: Oh, I'm sorry. Yeah, this slide was shown earlier, but I think it was also announced just with a caveat that the FDA hasn't had time to review these data, so I apologize for that.

Anyway, one of the other cuts we looked at was the presence or absence of protocol deviations. Another one was whether the lens was according to protocol, and as you know, most of them were not. Of the 194 data points, we had -- looks like about two-thirds of them were not.

DR. EYDELMAN: Sorry to keep interjecting, but my team just pointed out that I believe you misspoke. It's not that the FDA hasn't had time to review this data. This data was never submitted to the FDA.

DR. SMITS: I guess it was never formally submitted. I

apologize. Okay. Then I stand corrected.

Anyway, so we have these various cuts of the data, and as the FDA statistician pointed out, the study was not designed to have power to look at subgroup, mixed subgroup comparisons. And as any statistician knows, the absence of significance does not imply equivalence.

Anyway, we can still -- we have a reasonable sample size here. We have close to 200. We can see that the confidence intervals do largely overlap. And I'm not denying that if we had a sample size of 500 or 1,000, we'd start to see significant differences. But I think if you look at the spread of the confidence intervals and the difference in the point estimates and look at the base of the x-axis, we're talking about, you know, a fraction of a MRSE point. So the full range of the base, the x-axis is -.4 to +.4, and you can see the data do not encompass that whole range. They're basically encompassing approximately .4 of a diopter of MRSE.

DR. SCHALLHORN: And this is Dr. Schallhorn. Let me just jump in here, I think, because that's part of the point. Listen, the study was not, as Dr. Smits mentioned, the study was not designed to do sub-analysis. I agree with that. However, take a look at this chart. Take a look at the in-window visits and compare them to before and after. Look at the major protocol deviations. So when we exclude, when you exclude using the protocol-approved lens, you see that, based on the scale, there's almost no effect. So even if you don't talk about the statistical differences, there's still almost no

effect that these changes have. The scale, every mean there is plus or minus .2 diopters. I think that's probably the most important point.

Anyways --

DR. HIGGINBOTHAM: We have a comment and a question from Dr. Chappell, and I guess Dr. Chappell, if you could also translate for our representatives on the Panel who may not have seen data like this before -- I mean, with the caveat, certainly, this has not been reviewed by the FDA, but since it has been part of the discussion, just so that they can actually put this in their own heads.

DR. CHAPPELL: Thank you. So this relates to my earlier comment concerning how worried I would be is directly related to what the consequences are of the missingness or of the before, in, after window, the delay or premature measurement, and what the differences may be. So, for example, in a sensitivity analysis like this, if you found that the afters were significantly different than the in windows, then you're combining apples and oranges, and it would be very hard to interpret them. And it would be very hard to delete them, too. You'd wonder what was wrong with those patients that they were delayed.

So this kind of sensitivity analysis, it's a kind of subgroup analysis where you just look at the differences and hope that you don't see one, for the sake of scientific homogeneity. It's a special kind of subgroup analysis, however. Suppose we were trying to look at differences by gender

or race, and there were tiny groups. We would criticize those who conducted the protocol if that's what it was supposed to do, because he wouldn't have a big enough sample size.

Here, I'd like to point out that small sample sizes are good. That's what you want, right, because -- at least not in-window. You want small sizes of the violations. So the fact that the sample sizes are too small to make a powerful statement, which they are, can be considered a good thing, right? If they were zero, you couldn't make any statement at all in the before-window and after-window, for example.

DR. HIGGINBOTHAM: But we've heard previously about the lack of the fact that the study wasn't powered to do these sub-analyses. Can you put some context around that previous comment?

DR. CHAPPELL: I haven't seen the protocol, but there seems to be no interest in sub-analyses by the usual race, gender, age, et cetera, groups. And if there were, then the study would be too small. But for this kind of sub -- these are not the expected kinds of sub-analyses. These are kind of salvage sub-analyses. And for that purpose, like I said, you want the groups to be imbalanced and small. I mean, you wouldn't deliberately sample people before and after.

DR. HIGGINBOTHAM: Okay.

DR. CHAPPELL: I hope that helps.

DR. HIGGINBOTHAM: Any --

DR. CHAPPELL: And also I had a question. On subsequent slides -- I know what that vertical line, the dashed line is there for obviously. And then the next one, on manifest cylinder, there's a dashed line at .5, which seems to be also a reference value. But in future slides, there are vertical dashed lines which I don't understand. So slides -- it's cut off. That's slide 21 and slides 23 and 24, for example, have vertical dashed lines, which I don't know. Yeah, like that one. Why 70? Is that some kind of standard?

DR. SMITS: Gerard Smits speaking. That line represents the overall group effect for those with all data points. So the 194, the point estimate was at 70%, so we dropped the line down as kind of a reference for the whole group.

DR. CHAPPELL: Okay. It doesn't look exactly that way, and neither do the following ones, but I suppose --

DR. SMITS: I think that's the way the line has simply been drawn, not accurately, but it should be right in the middle of the box.

DR. CHAPPELL: Okay. Thanks.

DR. HIGGINBOTHAM: Sponsor, do you have any other points, I mean, because we're spending a lot of time on these data that have not been formally submitted, so I think we're kind of getting a little off track here. So if we can get back on track related to the data that are relevant to the questions that this Panel have to respond to later.

DR. SCHALLHORN: Yes. Dr. Schallhorn. And I agree. Another

point that was brought up was rotational stability. So if I can have CE-50? You know, a lot has been discussed about rotational stability, and I'd like to give some perspective to this also.

So rotational stability, the assessment of rotational stability was looked at in many different ways. It's important to realize probably the most important way is to look at how stable everything was. And I showed this slide before. The mean cylinder was stable throughout -- from one week on. If the lens was rotating, if there was a systemic rotation of the lens, if the lens was rotating vertically, you would not see that stable cylinder. Likewise, the uncorrected visual acuity remains stable, and patient satisfaction did not decrease, as you'd expect, if there was some issue with a rotationally unstable lens.

And now if I could go to -- yeah.

DR. HIGGINBOTHAM: This is Eve Higginbotham. Before you leave that slide, we learned that there were 11 patients noted at the last visit with some rotation. Are those 11 patients part of this 95?

DR. SCHALLHORN: No. I think -- Dr. Schallhorn again -- I think what that was was patients that had -- if you intended to put the lens in a certain fixation angle and then you looked at that one-year postop, did you put the lens in properly at that fixation angle or did the lens rotate? It could be a combination of the two. Where should I have put the lens, and where did it end up a year later? Where should I put the lens, and where did it end

up a year later. So if it's misaligned, you could have put the lens in incorrectly, right? The surgeon has an error in putting in the lens, or it could have rotated, those two things. So in other words, it's not rotation of the lens. It's a combination of the fixation, how well it was fixated at the proper angle, and then perhaps any rotation. So that 11 came from that aspect.

Does that answer your question?

DR. HIGGINBOTHAM: I'm going to yield to Dr. Macsai, because she has a burning question.

DR. MACSAI-KAPLAN: Dr. Schallhorn, there is an inherent "we don't know" here, which is I think what's made us all a little bit uncomfortable, because we don't know if the ways these last visit angles were measured is valid because this, you know, estimating the clock hours is not really a validated technique. And we don't know if there's rotation, as you said, or if they were misaligned when they were placed.

The reason that is of concern, obviously, is not just efficacy, but you all are the most experienced surgeons out there, right, in placing toric ICLS. So, always, we have the concern that when we have the beginner surgeon, their results could be different. So if you intend to put it at 15 degrees and inadvertently somehow put it at 35, but you get a good refraction, do you leave it at 35, you know? It begs the question of how accurate. It's sort of like strabismus surgery is how I'm beginning to wonder, because, you know, 5 and 8, 8 and 8, they all seem to work.

What exactly should we be telling surgeons to do?

DR. VUKICH: This is John Vukich, and I was the medical monitor for the clinical trials and did the education for the surgeons. In point of fact, we were all beginners, and this was the first use of the Toric ICL in the United States. This was a decade ago, so none of us actually had experience with this.

And understand that the use of toric IOLs was actually in its infancy at that point, in general. So the whole concept of marking ahead of time -- we understand that you have to sit the patient up in a slit lamp and do a mark that's just precise, and quite honestly, the techniques and the understanding and the precision of that wasn't fully understood or fully developed, for that matter.

So there could have been the introduction of error in simply as much as the degree that the mark on the sclera ahead of time before you laid the patient back could have introduced, you know, as much as 5 degrees of cyclorotation. We understand that now, and the surgical techniques have gotten so much better because we do understand how to put toric lenses in from the intraocular IOL standpoint.

So that part of it is definitely part of our learning curve, and I think it is reflected in the accuracy of the attempted, or at least the intended versus the achieved. And so there was some error -- not error as much as there was -- it wasn't as precise as we think we have gotten now, or maybe

even the understanding of how to make it as precise as it needs to be. These things have gotten better.

DR. MACSAI-KAPLAN: So --

DR. HIGGINBOTHAM: Dr. Macsai?

DR. MACSAI-KAPLAN: In follow-up to that, as I asked the FDA, if there is no evidence of zonular disruption, it seems there isn't rotation. I mean, if this thing is rotating, flopping around in there, there is going to be some zonular damage from where it's sitting. So that's why I'm asking that question about zonular disruption.

DR. VUKICH: John Vukich. If could answer that, there have been no cases of IOL -- ICL dislocation in the primary cohort or in the follow-on study of the Myopic ICL nor were there in the Toric ICL. I think what we have is a certain level of uncertainty, one with the measurement technique, which quite frankly has evolved since we did this, and the protocol was approved on how we did it. We would never do it that way again, obviously, but at the time, it's how we did it.

As far as, you know, is it flopping around, boy, that just sounds terrible, but you know, I mean, the reality is that, you know, it would show up somewhere else, and it's not showing up anywhere else. We can't prove beyond a shadow of a doubt, but maybe to some reasonable level, and I think maybe that's the burden that we have to come to, is this -- are we reasonably assured that it's efficacious? I think we've met that standard. Are we

reasonably assured that it's safe based on the parent ICL, based on the data we see, and I think we've met that standard, flaws and all.

DR. SCHALLHORN: Dr. Schallhorn, if I could just add one quick thing, and that is, you know, the methods that were used were the methods used. And while there were imperfections in where do I want to put this lens and how do I rotate it, these are the results we got, right? These are the results we got with it. And the results are good. Like I said, the data is strong. We're taking -9 diopter myopes with 2 of cylinder, and we're getting the majority of them 20/16 uncorrected.

So getting back to stability, so the refractive results, the acuity results all show stable, and then the direct measurement, for all the issues that the direct measurement may have in the assessment on a slit lamp, the lens was rotationally stable. Now, I would submit that if the lenses were rotating or spinning, they would be immediately apparent to a surgeon looking at the lens with a slit lamp. These lenses, I think, these surgically, when I looked at these lenses, they were stable. And that's showing up here.

And the last thing on stability, just to mention, there was some discussion about, you know, error of angle and vector analysis in that regard. And so I'd like to have Dr. Ed Sarver just briefly talk about his analysis looking at error of angle measurements when you consider the error of measurement in the error of angle assessment. And I think Dr. Hilmantel talks about that, too.

I think this is it right here.

DR. SARVER: This is it, okay.

DR. SCHALLHORN: Yeah.

DR. SARVER: Hi, Ed Sarver, optics consultant to STAAR Surgical. I just want to make a couple of comments about the error of angle analysis for rotation stability. The error of angle is a function of the intended and achieved refraction vectors. And so it's very dependent upon your measurement of refraction, which we know is noisy. And it can be actually very sensitive depending on the relative value of those two vectors. So whenever you consider the error that's possibly in your measurements could be plus or minus, for example, a ¼ diopter, then you get these kind of results. So we can say that we have on the order of 95% of all Toric ICL cases are consistent with the rotation of less than or equal to 5 degrees. And also, almost 99% that are consistent with the rotation of less than or equal to 15 degrees. And, again, what that requires is that you consider that the noise measurements can be within a ¼ diopter of the as-recorded measurements.

DR. SCHALLHORN: Okay. Thank you, Dr. Sarver.

So everything points to the lens being stable, I guess is the point that we're trying to make. Everything points to the lens being rotationally stable.

Anyways, another point that was discussed earlier is the secondary surgical interventions. And I'd like to ask Dr. Vukich to address

that.

DR. VUKICH: Dr. Weiss had raised the question of the secondary surgical interventions in the parent Myopic ICL study. And I know there was a slide generated -- thank you -- that looked at the one-year incidence of secondary surgical interventions. We had originally presented the five years, thinking that was the most complete, but to compare apples to apples at the one-year timeframe, you can see that the interventions of repositioning were .5 versus .8 at one year. I just lost mine -- okay, 1.9 versus .8, TICL versus MICL. There were no retinal detachments at the MICL in the first year, no cataract extractions done. So they are roughly comparable. Perhaps, you know, because of the sample size, replacements and/or removals were at a higher percentage. But we can take a look at the replacements or removals in the Toric ICL. So the overall incidence at one year was 1.6% at the toric -- or for the MICL parent lens.

And, of course, talking about the standards that have been developed, when we take a look at these lenses, there are a few of these secondary interventions that I think are just inherent to the patient population. Retinal detachment, I don't know if there's any way you can mitigate that. These are highly myopic patients, and I think we can say that that's an issue, but clearly something that we don't believe is related to the lens. The very nature of a toric lens means that there has to be positional accuracy, and some of that's going to be repositions. And so I think inherent

in this is going to be some assumption that there will be potentially reinterventions. And we've seen this here. At what level does it reach a critical concern? And I think that's a decision that the Panel will have to debate on whether or not these standards that are set are actually truly applicable for a toric lens even though they have been, to my -- thank you for educating me on that -- they have recently been approved for that. But I think maybe Dr. Price would like to maybe make a comment on that as well.

DR. PRICE: I'd just like to comment on the relative intervention rate versus cataract surgery. And in cataract surgery, we have a pretty high threshold to go back and do anything. You don't worry about vault. We're not doing iridotomies. And you don't go back unless they're off probably 3 or 4 diopters, whereas here, you know, the margin of what people want and what we're trying to do is a lot more critical. These are younger eyes. If there's a problem with a vault, we're going to go in and fix it.

DR. SCHALLHORN: Dr. Schallhorn again. Another point that was brought up was the endothelial cell loss over time, tracking it, the change in time, the bi-exponential, and so I'm going to turn that over to Dr. Price.

DR. PRICE: I want to answer Dr. Glasser's question, which was really good, and if I could have the slides up, if we could push that. This goes back and shows the original scatter plot, and you had asked if we had looked at each year, and if it changed over each year. It's important to look at this and realize that we can only do that for the first two or three years because,

remember, this was a sub-study that was only going to be three years long, and then later on, the FDA came back and asked us to do it to five.

So if we look at the cell loss, it was 3.2% the first year, 3.2 the second, 2.3 the third year. And then when we get all the follow-up in, we can't really do the years in between because they didn't all come in at those points. It was 2.4 overall. So I think there's really good assurance that the rate of loss decreases with time.

If I could have the next slide -- oh, I'm sorry -- go back.

DR. HIGGINBOTHAM: Last slide, Dr. Chappell --

DR. CHAPPELL: May I make a comment on that? Because I doubt that very point because the bi-exponential model is a sophisticated way of modeling first -- it's hard to see there, and the printout slide that I have --

DR. PRICE: This is not the bi-exponential.

DR. CHAPPELL: Okay. But even if you did that, there's a rapid initial loss?

DR. PRICE: Yes.

DR. CHAPPELL: Well, I mean 3%, but that's just one time. And then it stabilizes, but it seems to stabilize not at a decreasing loss rate, but at a consistent loss rate. You have a line --

DR. SCHALLHORN: Can we show you the bi-exponential model --

DR. CHAPPELL: -- that keeps going -- yeah, that's slide CP-16.

DR. SCHALLHORN: This is the --

DR. CHAPPELL: Right. And even the bi-exponential model has a fairly constant loss rate, which does not look alarming at eight years. And I know the dangers of extrapolating, but we have no choice here.

DR. PRICE: Right.

DR. CHAPPELL: We're talking about 2.2% per year, roughly, versus .6% per year naturally. So what happens when you multiply those by 20 years?

DR. PRICE: Well, the bi-exponential, we're going to have another slide after this, but bi-exponential, what it does, you're looking more at half-life. And so this graph and this calculation had a half-life of 33 years, meaning that the, you know, cell count is going to decrease by half at 33 years. Another 33 years, it'll go down another half. So if they start out at 3,000, this would estimate they'd be at a cell count of 1500 at 33 years later, and then at another 33 years, they'd be down at 750.

DR. CHAPPELL: Okay. But that is extrapolating. If we take it linear, which that looks like -- that could be bi-exponential, but it certainly could be a straight line -- you could also multiply that, the 2.2 times 33 years, and you get more than 50%. You get two-thirds.

DR. PRICE: Well, that's because we think the amount is decreasing over time.

DR. CHAPPELL: All right. But my point is not to contradict you but to say that graph does not show that. I don't see it at least.

DR. PRICE: It's hard to see.

DR. HIGGINBOTHAM: Dr. Glasser has a question.

DR. GLASSER: David Glasser. Thank you for the discussion, Frank, and Dr. Chappell.

You know, the reason I asked that question was specifically because I was wondering whether this is really bi-exponential or if really what's happening is you have a discrete cell loss at the time of surgery followed by a linear cell loss afterward. That was really what my question was trying to get at. And I'm not sure that you have enough data to really tell me for sure whether that 2.2% is becoming less and less over time or if it's going to stay 2.2% from 2 to 5 to 10 to 20 years.

DR. PRICE: The only one we have longer follow-up on is the outliers, out to 15 years. That has not been reviewed by the FDA.

DR. GLASSER: So then the corollary to that is if we assume the worst-case scenario and that it stays at 2.2%, and then are we picking a cell density for entry into the study or for being a candidate for the surgery that's high enough --

DR. PRICE: Sure.

DR. GLASSER: -- to give you a reasonable cell count 35, 40 years later, which is about the average life expectancy of someone who has a

surgery?

DR. PRICE: With permission of the Chair and the FDA, I can show the worst-case scenario, the outliers, and data out to 15 years.

DR. HIGGINBOTHAM: If it has not been submitted to the FDA formally -- you're nodding your head yes -- Dr. Eydelman?

DR. EYDELMAN: You can present the data, but with the understanding that it hasn't been submitted or reviewed by us.

DR. PRICE: It's not the next slide we had up, but yes, this one. Oh, I hit the clicker here. So earlier today, I showed you -- there's three parts here, the first two parts, and these are the worst case. You know, the outliers, as I said, were three standard deviations off the rest. And there was 5.9% the first 5½ years, and then the second segment, it was 3.7. And then the last ones, these, I want to point out, they were hand counted at one site, Dr. Vukich's. He saw these patients back in. And these data points are at about 15 years. They weren't done at the reading center. But what they do show us is that there's a leveling off. And these are the worst cases. Early on, we had the case of trauma at a year with somebody, the large cell loss, and then certainly the ones that lost it at surgery. But I think these are hopeful. And, actually, looking at these is what had me start to look at it as a bi-exponential function, because I think this is the kind of pattern we're seeing, that there's not an ongoing damage going on.

And then if I could have the third slide that I was going to show

before. Now, when we look at our dataset here, we have a lot of lower cell counts that actually wouldn't be receiving these lenses at this time. And let me do this. So after this study was completed, they came out with the ANSI standards, and these are calculated so that by the time someone reaches 70 years of age, they're left with a cell count of 1,000. And you have to have a pretty high cell count if you're going to get this as a young person. And this is all with the labeling. And so this gives some added safety, that people have to have a sufficient cell count to give you a margin of safety here. But this is definitely an area that, you know, needs more evaluation with the future.

DR. HIGGINBOTHAM: Well, is it about this point that -- I have Dr. Saheb first and then you, Dr. Chappell.

DR. SAHEB: The 2.2% decrease over time, is that including the 10 discussed outliers?

DR. PRICE: It was 2.4, I'm sorry.

DR. SAHEB: The 2.4 --

DR. PRICE: We've gone through the data so many times. I'm sorry. It was 2.4.

DR. SAHEB: And that includes the 10 discussed outliers?

DR. PRICE: Yes.

DR. SAHEB: Do we have a number excluding those?

DR. PRICE: We do. I'm not sure I recall what it is right now. It gets better by a couple tenths.

DR. SAHEB: It's less than that?

DR. PRICE: Yes.

DR. HIGGINBOTHAM: Dr. Eydelman -- excuse me, Dr. Saheb, Dr. Eydelman has a comment.

DR. EYDELMAN: I hate to keep belaboring the point, but this slide doesn't denote the fact that this was never submitted to the FDA either.

DR. PRICE: Oh, I'm sorry. This was not submitted to the FDA. I apologize. Yes, there's one, okay, one more that I can show here.

DR. HIGGINBOTHAM: Was it submitted to the FDA?

DR. SCHALLHORN: No, this was not submitted to the FDA.

DR. PRICE: They have the dataset, but they haven't seen the analysis. This breaks down excluding outliers, to answer your question. First year, 3.3, and then 2.1 per year after that.

DR. HIGGINBOTHAM: Okay. Dr. Chappell, and then we'll have Dr. Huang.

DR. CHAPPELL: Thanks. Could you back up a couple slides to the outliers issue, the ones in which you have 15 years follow-up? So I hate to belabor a statistical point especially since I don't -- I'm not the right one to say whether it's clinically important or not, but the fact that you see that leveling off in the red curve, I believe, is an artifact of the sampling. So am I allowed to leave the microphone and get up and point? I probably -- I can?

DR. HIGGINBOTHAM: It's a free country.

DR. CHAPPELL: All right.

DR. HIGGINBOTHAM: Yes.

(Laughter.)

DR. CHAPPELL: So I'll speak loud. So suppose, and I'm not saying it's true, but suppose that this black linear line, this line is the case, and this is kind of debate, and there's no leveling off at all. And so if we did follow up all these patients, we would have this big mass of points just following this line, right? But then you pick out the outliers only -- select to follow up, and those are the ones on the bottom. Geometrically, you have to end up with this kind of curve because you're picking the lowest ones here. So, paradoxically, by picking the worst ones by 10 to 15 years, it makes it look like things are leveling off. But it doesn't mean that they'd all level off. It just means that's the pattern. So there's no substitute for full follow-up on all of them or your expertise in whether you think this will continue to go down and how important it will be. Thank you.

DR. PRICE: I think those are good observations. But let me tell you why I don't agree with them. The dataset that we have was what STAAR was requested to do by the FDA, and so there's limitations with it, but it's, you know, it's what we have. I can tell you in my experience that when I have individuals that have an ongoing problem, such as a glaucoma tube, some chronic problem with an intraocular lens, it doesn't level off. It keeps going down like a submarine. And sometimes the decrease accelerates.

So one of the big concerns with these, especially with the first five years, is, is that going to be a submarine type thing, where it just keeps going down to the bottom? But at least the data that I see here doesn't look like an ongoing problem. Does that make sense or not?

DR. CHAPPELL: Oh, certainly. Expert opinion is relevant.

(Laughter.)

DR. PRICE: Okay.

DR. HIGGINBOTHAM: Okay. Thank you.

On that note, let's move to Dr. Huang.

DR. HUANG: Well, I think, you know, there is still ongoing debate about the validity of the results, and we're certainly not going to argue over, you know, that the safety or efficacy, you know, based on what you presented. But I was just very perplexed that, you know, on the proposed indication it ranged from, you know, -3 to -20. And then, you know, on the proposed, the model, there's only -3 to -16. So based on the subset and even though we don't have enough subgroup analysis, do you have enough data to pick you up in that, you know, missing -16 to -20.

DR. VUKICH: This is John Vukich. The -3 to -16 would be for the elimination of myopic astigmatism. From 16 to 20, the indication would be for the reduction of, and that would be consistent with the Myopic ICL parent lens. And --

DR. HUANG: Your lens is only -3 to -16, so you don't propose to

fully correct those patients from -15 to -20 --

DR. VUKICH: Correct. It would be -- we would request labeling to reduce myopia. So if someone who was -20 and who was left as a -4, I think, would have a substantial improvement in the quality of their life. You saw a photograph of what a -20 lens looks like. That happened to be a picture of glasses from one of my patients, and that is a -20 lens. It's a substantial burden. You take them to -4, and these patients are certainly improved.

DR. HIGGINBOTHAM: Did you have a follow-up, Dr. Huang?

DR. HUANG: No, it's okay.

DR. HIGGINBOTHAM: You can come back. Okay. This is Dr. Higginbotham. I have a question about the patient satisfaction instrument and your results. And I'm looking at slide CS-39, page 20 in our books that you gave us this morning. And I notice that at 12 months, there certainly are a significant number of individuals that attest to night vision difficulties and night driving difficulties. And, you know, recognizing that at night, you know, it certainly has a tendency to bring out the most significant issues related to any optical device.

And given the fact that we understand that your instrument didn't really test for a spatial disorientation as one of the concerns, first of all, can you comment on, you know, the severity of those night vision difficulties that came out of your instrument and then any concerns you may have about

missing any spatial disorientation issues? And the last question is whether or not there was a continuation of this frequency of complaints around night vision and night driving. Does that increase over time?

DR. VUKICH: This is John Vukich. So when we looked at patients' subjective assessment of their symptoms, we gave them a questionnaire, and you can see in the gray bar was their preoperative and in the blue bar was the postoperative. There were two different things that we could look at. One was what they considered symptoms, and the other was what they considered as disabilities related to just vision quality.

So if we do look at glare and halos, although it would appear as though there is some increase from baseline -- and by the way, these patients, these are moderate, marked, or severe. So we lumped anything in that seemed like it was moderate or worse all together. So it was kind of a full -- anyone who had a complaint that reached the moderate level, we put them all in. The glare, then, it seems like there may be some increase if you look at it, and maybe there's a signal there, but it didn't reach statistical significance when we did that.

Now, the other part of the equation is, well, how did it influence their own assessment of their ability to perform tasks. And there were two things that we asked. One was night vision difficulties, a rather broad question to ask, and the other was very specific, night driving difficulties. And you can see there they're very evenly matched in terms of

their assessment of their ability to perform tasks under those conditions and specifically drive a car under those conditions.

DR. SCHALLHORN: Dr. Schallhorn. I would just add that nothing would indicate from this that there's a problem with the lens in that regard.

DR. HIGGINBOTHAM: This is Eve Higginbotham. Can you comment on the validity of the instrument that you used as well as the absence of testing for spatial disorientation -- distortion, I should say. And then a question I didn't ask, what about the people that didn't respond to the patient satisfaction questionnaire? Do you have a sampling of what their results are if they were tested?

DR. SCHALLHORN: This is Dr. Schallhorn. The questionnaire was not a validated questionnaire. So there were really no instruments -- it was not common practice in these clinical trials to use a validated questionnaire at the time. Obviously, that has changed now, and we know a lot more about patient-reported outcomes. The tools that we have now are much more sophisticated in that regard, but this is what was available at the time.

Regarding spatial distortions, or whatever, it was not asked in the questionnaire, so I can't directly comment on it other than saying that, you know, my -- that with a very high level of patient satisfaction and seemingly very low level of these difficulties with night driving, issues like

that, that I would not expect it to be a significant problem, this spatial disorientation.

DR. HIGGINBOTHAM: And what about the patients that we noted that did not respond to the initial questionnaire or instrument? Was there a follow-up to try and get responses from those individuals?

DR. SCHALLHORN: Well, this is Dr. Schallhorn. This is at 12 months postop. And you can see that the *n* preop is 210, the postop -- they're missing 16 at the 12-month exam. So the sample size is not -- the missing data is not greatly reduced at the 12-month visit in this case. And so I would not expect an issue with those small number of patients in that regard. The patients, by the way, they were -- these were the patients that were missed, lost to follow-up or discontinued.

DR. HIGGINBOTHAM: This is Eve Higginbotham again. So we don't know if they are just totally unhappy somewhere or totally happy somewhere out there with their lenses? I guess that's the point.

DR. VUKICH: Of course, that would include, well, one patient we know who missed, lost, or discontinued, so some of these were no longer in the study, and it wasn't that they didn't show up, as they were discontinued from the study. So I guess there will have to remain some level of uncertainty about how that group of patients might have reacted.

We can certainly look at the satisfaction data, however, if that would be of interest. And this, then, would probably, I think, at least shore

up or corroborate the lack of change in the marked, moderate, or severe symptoms. And then we look at patient satisfaction with surgery, and we can see that, at 3 months and at 12 months, patients were very satisfied, very extremely satisfied over 95% of the time.

DR. HIGGINBOTHAM: Thank you. We have three Panel members that'd like to speak on this or another point.

Ms. Schwartzott?

MS. SCHWARTZOTT: Hi, Jennifer Schwartzott. On that slide that was just up, I have all of those symptoms that are on there, the night blindness, the night driving issues, and it is severe, but it is also more of a annoyance, a bother. To me, that is not considered a severe symptom. That's just from my own personal perspective of having every one of those, and that would not keep me from having my other eye done for sure. To me, that's just a bother, but it's not severe.

DR. HIGGINBOTHAM: Thank you very much.

Dr. Saheb?

DR. SAHEB: Another way to address this concern could be to look at at least the visual outcomes of those patients who did not answer the questionnaire. Is there a significant difference, or a trend at all, between those patients who did not answer these questionnaires and those who did? And that would allow us to extrapolate a little bit.

DR. VUKICH: Dr. Vukich. I'm afraid it may be sort of late in the

fourth quarter to generate that analysis, but we certainly could, and it could be a point of discussion with the FDA in a labeling situation.

DR. HIGGINBOTHAM: Thank you.

Dr. Chamberlain?

DR. CHAMBERLAIN: And just to add on that, I wonder if there's a correlation with scotopic pupil size, which sometimes we focus on for other refractive candidates, a lot of discussion in the literature. In this case, I'm wondering about optic sizes that go from, I think, 4.9 to 5.8. So if you had a patient who had an 8.0 scotopic pupil, you know, would you still confidently put this lens and then advise them that they're going to fit into this category of nighttime halo and glares?

DR. SCHALLHORN: This is Dr. Schallhorn. Well, in the study, they did not measure the low-light pupil, so we don't have that to correlate. But if you saw -- if you recall on that chart, the percentage of patients that had these difficulties at night and night driving were the same as it was preop. So we can't answer that question about pupil size in that regard.

Based on the preponderance of peer-reviewed literature, my own experience regarding LASIK and pupil size, we don't find a correlation with modern LASIK and the size of the low-light pupil in that regard.

DR. VUKICH: And this is Dr. Vukich, medical monitor for the trial. Ironically, the only pupil issues that were entry criteria was they had to be able to dilate to 8 mm in order to be enrolled because we had to have a

big enough pupil to get the lens posterior to the iris plane. But we certainly did not see any -- we don't have the analysis to show, but we did not see any correlation with pupil size, and it's very consistent with the experience in LASIK.

DR. CHAMBERLAIN: Just a comment on that. In the refractive patients, the optical zones and the cornea are bigger than the optical zone in the lens, so obviously in a different location as well, so it may not be comparable directly.

And I guess the other question along the same lines, although I think I know the answer, is we've talked about rotational stability. Is there any observation of the lens just being off-center slightly?

DR. VUKICH: We did not have any instances in which there was decentration of the lens, and so the optical center was displaced from what you would expect to be the geometric center of the lens. I mean, there are some situations where there's a slight eccentricity of the physiologic pupil being eccentric to the geometric center, and the lens does center equally because the footplates are equidistant. But there are no eccentricities to the lens that we've noticed, or noted, seen.

DR. HIGGINBOTHAM: Any other -- oh, yes, Dr. Weiss?

DR. WEISS: So I may be looking at something different than what you're describing, but in table 46 in moderate and marked reported glare preoperatively, it's about 14%, and then at 12 months, it's about 20%.

So I understood you to say that it didn't change with time, but with this, at least with moderate and severe, it's gone up significantly after the IOL.

DR. VUKICH: And I'm sorry if I didn't make that clear. There may be a signal there. When we ran statistics on it, it didn't show up as statistically significant. So there is a difference on those two metrics that were tested in terms of the absolute numbers, but when we ran statistics, it didn't come back.

DR. WEISS: And that's where my concern goes -- gets repeated in the validity of the data is the not reported is 9 at 12 months. So the repetition of data that we don't have, you don't know which way it's going to go. And so our reassurance goes down.

With the transillumination, I had -- did I misunderstand that there was no transillumination in this or --

DR. VUKICH: I'm sorry. That was confusing in how it was presenting. A transillumination was not reported as one of the fields that we looked at in the Toric ICL study, so it was not the issue. So if we heard no, it was either misspoken, but the answer should be it was not looked at. It wasn't --

DR. WEISS: No problem. Okay. Thanks.

DR. VUKICH: -- as a safety analysis one of the metrics.

DR. HIGGINBOTHAM: Any other questions from the Panel for -- Dr. Huang?

DR. HUANG: Andrew Huang. And this is a follow-up of a question from earlier this morning. I was just wondering, you know, since there are so many -- so much enthusiasm from the community surgeons, but there are also a very -- a wide, you know, international experience. Is there any, you know, peer-review article or anything talking about the safety or efficacy of the Toric ICL in the literature with the large-scale and pertaining to some of the questions we are asking?

DR. VUKICH: This is Dr. Vukich. In the analysis that the FDA prepared in the Executive Summary, they went through and did an exhaustive literature search, and then they identified 43 articles that they felt met the standards for data extraction. And within that, there is a fairly large body of data, several centers with, you know, shorter and longer follow-up, as you might expect. But perhaps even Dr. Eydelman would like to help us with this one.

(Laughter.)

DR. EYDELMAN: Yes, actually --

DR. HIGGINBOTHAM: Dr. Eydelman?

DR. EYDELMAN: Thank you. Dr. Eydelman. Actually, I wanted to clarify that our analysis had to do with MICL, not TICL. We did not identify sufficient literature to review with the current version of the TICL.

DR. VUKICH: Okay. I'm sorry. I misunderstood the question. It was the ICL platform in general that's had a lot of experience, and there are

many articles on the Toric ICL study as well. And those were included in the literature. So I'm not sure that the 43 were only MICL, but there certainly is literature on this. And I guess we're not prepared to show you an abstract of that, but it's certainly available.

DR. HUANG: You know, in that line, you know, the data is somewhat weak, you know, and then we only present, you know, 210 eyes.

DR. HIGGINBOTHAM: Any other questions?

Dr. Zabransky?

DR. ZABRANSKY: Yeah. The FDA earlier today mentioned something about an oval presence of the lens, or something of that nature. And their particular presentation indicated that the lens itself might become detached at the corners. That would be a contraindication for the use of the lens?

DR. SCHALLHORN: Well, this is Dr. Schallhorn. I believe you're talking about how the internal structure of the eye may be a little longer vertically than it is --

DR. ZABRANSKY: Yes.

DR. SCHALLHORN: And when we looked at, again, rotational stability, we don't see the lens -- we see the lens being rotationally stable regardless of the fixation angle. And so regardless of the angle, 0 to 22½ degrees, we don't find that the lenses that are put closer to 22 degrees have a tendency of rotating vertically like you would expect with that theory.

DR. HIGGINBOTHAM: Okay. Seeing no hands raised, Sponsor, do you have any other comments you'd like to make in the last two minutes?

DR. SCHALLHORN: Yes. This is Dr. Schallhorn. A quick comment. There was a discussion about the manufacturing plant, and I'd like Mr. Hughes to discuss that very briefly.

MR. HUGHES: Yes. We had a GMP audit of our facility in Switzerland in August last year, and there were three findings. And shortly after the audit, we received a letter from the Division of Enforcement, i.e., Office of Compliance, which says that while deficiencies were observed during the inspection, it does not appear to warrant consideration of regulatory follow-up at this time, and concluded that all of the corrections, corrective and systemic corrective actions will be verified at the next routine scheduled visits.

We have worked on these three areas that were identified, but based on this letter that we received from the Director of the Office of Compliance, we didn't believe we needed to follow up and provide this information to the Agency. It would be examined at the next routine audit. So it's not that we haven't responded. We've moved to action the CAPAs. We're just waiting for the next routine audit for that to be taken into consideration, as directed in a letter of the Office of Compliance.

DR. SCHALLHORN: And if the Chair would like, we could -- we have a copy of that letter from the FDA. We could enter that in the record.

DR. HIGGINBOTHAM: Does anyone on the Panel -- this is Eve Higginbotham -- like to have that seen in writing? Was it sufficient to have heard the oral presentation? Seeing no votes here, I think we'll just proceed.

Thank you, Sponsor, for your clarification of some of our questions, and don't leave the room yet, so we may have you come back. Thank you.

Panel, we have an opportunity to bring the FDA back if you have specific questions for the FDA. Keep in mind that if we bring the -- okay, well, keep in mind if -- when we bring the FDA back, Sponsor will have a chance to come back as well, so -- but we want to make sure that you have all your questions answered, as we can proceed more expeditiously through the Panel Questions if we have a full scope of understanding before proceeding.

So looks like FDA is coming back to the table. Please take your seats.

DR. EYDELMAN: Thank you. There are several points we believe need further clarification. So rather than interrupting the Sponsor, I asked my team to succinctly try to address these.

DR. HIGGINBOTHAM: Thank you, Dr. Eydelman.

While FDA is coming back to the table, Ms. Latimer, slide 48, page 24, I think is a nice diagram that illustrates the placement of the TICL. I think you had questions. And so if you have specific questions, using this

diagram, perhaps, as a guide for your questions, and maybe we can more specifically answer your questions as part of the Panel Deliberations.

MS. LATIMER: Thank you. Which slide was that, did you say?

DR. HIGGINBOTHAM: It's slide 48, page 24 of the FDA document, the stapled, not the nice glossy notebook.

DR. NGUYEN: Hi, this is Tieuvi Nguyen. I think we'll first start off by addressing the comments that were just made regarding the GMP inspection in Switzerland.

MR. PEREZ: Yes, this is Cesar Perez in Compliance. I just want to make a point that we sent a VAI letter after we reviewed the deficiencies, and we concluded that, yes, they were not as grievous as an OAI, which would result in a warning letter. However, we still believe that those three deficiencies needs to be addressed. And even though we don't need a response at this moment, like the letter says, we need to -- next time we go on inspection, we're going to look at those. Doesn't mean that the three deficiencies are not important to take a look at. Just wanted to make that point.

DR. HIGGINBOTHAM: Any other comments from FDA before --

DR. EYDELMAN: Yes, we do, but before our compliance colleague leaves, I just wanted to make sure so I don't make him pop up and down that there weren't any other questions about inspections, because the rest have to do with other aspects.

DR. HIGGINBOTHAM: Any questions about the inspections?

Dr. Zabransky, I think this was your domain.

DR. ZABRANSKY: No, the answers that have been given, both by the company and FDA, have been satisfactory. Thank you.

DR. EYDELMAN: Thank you.

Then proceed, Tieuvi.

DR. MOKHTARZADEH: This is Maryam Mokhtarzadeh, Dr. Mokhtarzadeh here. There were a few things I wanted to follow up on, and while Tieuvi is bringing up some slides, one point I wanted to make is regarding the 15-year endothelial cell data that the Sponsor showed, again, an analysis that wasn't submitted to FDA. But one comment I did make in my presentation is that one limit of looking at those outliers in later years is that from the data that was presented to FDA by the Sponsor, it appears that 3 of the 10 eyes had the ICL explanted between the 5-year and 10-year postoperative time period. Again, from the data that was submitted to FDA, I believe at least one of those eyes was included in the 10-year data presented on those outliers. So extrapolating to 15 years, we have even fewer subjects. And I can't tell you what percentage of them actually still had the ICL in place. So, again, that is a limitation.

In addition, the Sponsor did mention that those -- that endothelial data was hand-counted at the site, not at the reading center. We were dealing, as you all know, with an unmasked trial to begin with. So there

are multiple limitations to that data to be considered. We haven't formally analyzed it, but I just wanted to call your attention to those things.

So with regard to the safety profile, very early on -- I think it was one of the first questions asked -- Dr. Weiss asked us whether the safety profile of the TICL was expected to be the same as for the MICL. And I want to make sure, as I've watched the discussion progress over the course of the day, that our response wasn't -- that our response was complete.

So, again, as we said, the TICL safety profile was assumed to be similar to the MICL at the time of approval of the TICL study. That was the basis for some of the assumptions that were made by the Sponsor in the acceptance of those assumptions when FDA approved the protocol. But, again, they remain assumptions. The similarities we noted were that the ICL lens platform is the same. The differences expected at that time were the fact that the toric surface would potentially allow the opportunity for distortions due to axial misalignment, and in addition, we'd have to consider the potential for rotation of the ICL at the time of surgery and/or in the postoperative period, which obviously could lead to secondary surgical interventions, among other things.

So one thing I want to make sure that wasn't lost, which I went through during my presentation, is the fact that position and sizing are critical issues to the safety profile of the ICL. Both of these factors can change vault. And as we discussed, the amount of vault is relevant to the potential for

adverse events. If you can go to the next slide?

As I showed you with ICL position, there has been some evolution in thinking over the course of the TICL submissions from the protocol to the PMA with regard to the actual intended position. And as I noted in my presentation, the fact that, depending on which of these positioning targets you use, you could affect the lens vault and, in fact, increase the lens vault, as you see in the last slide on my slide. Next slide?

With regard to the sizing, again, in the protocol, they were collecting data on white-to-white diameter. In the study, some people used alternate sizing methods. In the labeling, recommendations are given based on white-to-white diameter. We all know the limitations of those. It also mentions that direct measurements should be considered as alternate methods. The implication of that statement now is different than it was perhaps a decade ago, with the evolution of technology. So I think there's one more slide relevant to this.

As I also mentioned, in the literature, this has been noted, the fact that there is some discrepancy in the sizing methodology used. So when we are asked about the safety profile of the TICL, as was stated previously, each PMA needs to stand on its own, and these are things that we do urge you to consider, in terms of giving this application a complete assessment by the Panel. These are not things that we intended to tell you to in any way ignore or minimize. We want you to be considering the safety profile of the

TICL.

Okay. And then one last thing I wanted to mention about the literature review, with regard to what was included in it, there was -- there were articles from both the MICL and from TICLs. But what I noted in my presentation was the fact that published literature may be reporting on U.S. or outside U.S. use of the device. With regard to the TICL, we would expect that, in most cases, it would be outside U.S. use, given that it is not currently on the market.

Furthermore, I said outside U.S. use could include other ICL models and sizing methods than those approved in the U.S. Therefore, you do need to take those under consideration with any literature that would have been included relevant to the TICL. We can't give you that assurance that the model or the sizing methods are relevant to what you are considering for approval.

That's all I had to say.

DR. EYDELMAN: Statistics --

DR. HIGGINBOTHAM: Any comments or --

DR. EYDELMAN: I'm sorry.

DR. HIGGINBOTHAM: Yes, Dr. Eydelman?

DR. EYDELMAN: We have one more topic. I don't know if you had questions about this, but our statistical colleagues wanted to make a comment as well.

DR. HIGGINBOTHAM: Can I ask Dr. Weiss to ask her question first, and then we can proceed with the statistical?

DR. WEISS: There was no confirmation of where the footplates were sitting, was there?

DR. MOKHTARZADEH: In the study? Let me just make sure I understand. You're asking me if there was any imaging to know where the footplates were sitting?

DR. WEISS: Yes.

DR. MOKHTARZADEH: That was not part of the study. As I mentioned, there were some investigators that used alternate methods of sizing, such as UBM or other techniques. Those were not part of the protocol, so I can't give you --

DR. WEISS: So how do you know where you put it?

DR. MOKHTARZADEH: That's an excellent question. I think that -- again, that was not part of the protocol. We can't really comment on that.

DR. HIGGINBOTHAM: Okay. Statistical discussion?

DR. QI: I'd like to make a further comment on the sensitivity analysis. I think I heard that the sample size of about 200 is big enough for the subgroup analysis. That's not true. Let me illustrate. Could you put the slide, sensitivity slides up? Let me pick --

UNIDENTIFIED SPEAKER: Their slide?

DR. QI: C-24, Sponsor, the applicant, C-24.

DR. EYDELMAN: We cannot project Sponsor's slides, You.

(Laughter.)

DR. QI: I'd like to make a comment.

DR. EYDELMAN: I would like to ask Panel members to open their packets for that slide.

DR. HIGGINBOTHAM: In the glossy notebook?

DR. QI: Slide CE-24. It's "Protocol Deviation Sensitivity Analysis," with a subtitle "Percent UCVA 20/20 or Better."

DR. HIGGINBOTHAM: We're there.

DR. QI: If you look at the before window, in window, and after window, before window, the point estimate, percent UCVA 20/20 or better is about 90%. In window, it is about 81%. And after window decreased to 75%. If you look at the sample size of before window, it is only 12. So we're talking about the sample size of 12 for subgroup instead of 200. If you look at the confidence interval, the reason why it is so wide is because the small sample size. If you increase the sample size, this confidence interval will shrink also for after window. So these three confidence interval will no longer overlap.

DR. HIGGINBOTHAM: And for those of us on the Panel that are not used to looking at the data, could you kind of provide some context for the significance of not overlapping versus overlapping?

DR. QI: Not overlapping means there is a difference. There

may be a significant statistical difference among the three groups.

DR. HIGGINBOTHAM: Yes, Dr. Chappell?

DR. CHAPPELL: I agree that if you increase the sample size from 12, that large confidence interval would shrink, but also, the center may well move. I mean, that's why we have large sample sizes in the first place. If we knew that the point would stay in the same place, then we wouldn't need to have a bigger sample size. So to me, the only evidence from that confidence interval is that cylinder change before might be a little bit lower, but there's absolutely no proof of it since it overlaps so thoroughly. And with a large sample size, you cannot say that the center will stay in the same place but the confidence interval will narrow, can you?

DR. QI: We expect that point estimate will remain the same, but the confidence interval would shrink.

DR. CHAPPELL: I respectfully disagree. That's why we have a large confidence interval, a wide confidence interval, because we don't know where the point estimate would be with a large sample size.

DR. QI: I think you said the small sample size is good?

DR. CHAPPELL: Small sample size is good when that represents mistakes.

(Laughter.)

DR. QI: Yes. So that's what I'm saying. Small sample size is bad.

DR. HIGGINBOTHAM: So we have Dr. Glasser, who is dying to get into this conversation.

(Laughter.)

DR. GLASSER: I'm with that guy over there. David Glasser. I mean, what evidence do you have that the point would change, that the mean would change, if you increased the sample size? I don't think you have any evidence for that. You don't know what the mean is going to be if you increase the sample size. That's the whole purpose of having a large sample size.

DR. QI: That's what Dr. Chappell said.

DR. GLASSER: Yeah, and I agree with him.

DR. QI: No, no, I mean the point estimate, there's no evidence that point estimate would change.

DR. GLASSER: Or stay the same?

DR. QI: Yeah, it may stay the same --

DR. GLASSER: It may --

DR. QI: -- but the confidence interval would change.

DR. GLASSER: The only thing you can say about increasing the sample size with any degree of certainty is that the confidence interval would most likely decrease. You can't make any statement about the likelihood of the point estimate changing or not.

DR. QI: But it is more likely that because of the confidence

interval shrink, there is a higher chance that the overlapping -- there is less overlapping.

DR. HIGGINBOTHAM: Okay. So you did have a slide that you projected before, and I guess I would ask, David, do you agree with his general points about sensitivity analysis? I don't know if you still have the slide that you presented earlier this afternoon.

Dr. Eydelman?

DR. EYDELMAN: For the sake of the time, I just wanted to make sure there's only one other point that stats wanted to make, correct? No? At this point, he no longer has a point. Are we done with our comments, then?

DR. HIGGINBOTHAM: Yeah.

DR. EYDELMAN: Okay. Thank you.

DR. HIGGINBOTHAM: So I guess I wasn't asking for another discussion, but whether or not you at least agree with these principles as presented here?

DR. GLASSER: Yeah, I agree with the principles that are presented on that slide, that an increase in the sample size may decrease to p-values less than 5%. But that's a "may." We don't know that, because we don't know if the mean is going to change.

DR. HIGGINBOTHAM: Thank you.

Was there anything else that FDA had to present, or if Panel

has any questions for the FDA?

Yes, Dr. Eydelman?

DR. EYDELMAN: I'm sorry. I believe Yao has one small point of clarification.

MS. HUANG: Yao Huang, statistic review with FDA. We just -- I wanted to add some comment about the worst-case analysis on endothelial cell loss presented by the Sponsor. Number one, we know ECD loss is a concern for the TICL. Unfortunately, we don't have data for that study. So we have to rely on the ECD loss data from the MICL PAS study.

And number two, because the worst-case analysis has not been reviewed by us, so we have to rely on the Sponsor's plot they just presented. Actually, our understanding is they have one or two models. Both models assumed the trend of the ECD loss over time. There are two stages. One is the chronic drop in the first -- very shortly after surgery. Then there is a chronic ECD loss over time, which is believed more relevant to the implantation of the device.

So the worst-case analysis, the red line they presented, was based on the bi-exponential model, and the black line presented in the plot was based on linear, piecewise linear assumptions. So that's why, as Dr. Chappell pointed out, so if you look at the trends of the two lines, they could present different outcomes in the long while.

Another comment we want to make is if -- even if we have to

rely on the ECD loss data from the MICL PAS study, so we still have -- we'd like to remind the Panel to be aware that the ECD loss, the trend of the ECD loss, may be different from the ICL. It could be better. It could be worse. We don't know because we don't have data.

DR. HIGGINBOTHAM: Thank you very much.

Dr. Weiss?

DR. WEISS: I'm very concerned that the Sponsor didn't give this material to FDA, so I'd sort of like to understand the protocol. Is there a deadline by which FDA has to get everything, or could they bring it to you even the day before?

DR. EYDELMAN: Okay. So as you've seen from our regulatory submission slides, the Sponsor had ample opportunity to present data to us. Having said that, they are free to present data at any point. That's why I was trying to delineate that the slides presented were never submitted, not just not reviewed by us. So to the best of our knowledge -- well, this is the first time we're seeing it.

DR. WEISS: Jayne Weiss again. So the rules of the game are if they wanted to submit data to you, they could have even done it last week or yesterday?

DR. EYDELMAN: Correct.

DR. WEISS: So that's of great concern to me.

DR. HIGGINBOTHAM: Okay. On that note, I'd like to thank FDA

for their clarification. I'd like to invite Sponsor back to the table to respond. I'd like to remind the Panel we have an hour and 15 minutes to go through our six questions and then finally vote, because we will be done by 6. So Sponsor is taking their seats at the table, and to be fair, you have up to 15 minutes.

DR. VUKICH: John Vukich. If I could respond to the timeliness of the sensitivity analysis submission, as you know, this Panel was originally to convene one month ago, and these slides were submitted at that time. So it was one month previous. Again, I'm not fully aware of the deadlines and the process involved.

I can respond to why wasn't it done earlier. You know, clearly, as we prepare the ability to respond and provide the best available data, it became clear that a forest plot of sensitivity analysis, which was presented but not reviewed, was, in fact, a good way to show what we felt was the case or felt the rest of the data supported, which was that this would not have an effect on the data and the overall ability to interpret the data. And this was yet another way to show that.

So this was, quite frankly, another analysis we did a month ago, and at that point, then, should we have thought of it three months ago? Probably. But here we are.

DR. HIGGINBOTHAM: Dr. Eydelman?

DR. EYDELMAN: Just to clarify, submission of the data means

submission under one of the supplements, and I'm sure that your regulatory collaborators are quite aware of that. What you're referring to is just putting it on the slides for presentation at the Panel. That is not submission.

DR. SCHALLHORN: Dr. Schallhorn. And just to reiterate, though, when this was looked at, issues like axis of the lens, the lens power deviations, to tell you the truth, I think that the thought a while ago, several months ago, was that there's such a compelling clinical, surgical argument that these shouldn't matter, that that's probably put us off from doing the sensitivity analysis and getting that submitted. In other words, you know, from my perspective, it's so -- you know, the -- again, as I've talked about, these different things were just so compelling that, well, that shouldn't matter, it does not matter clinically or surgically. And I think that's erroneously led us down the path of waiting until later before doing the sensitivity analysis.

DR. HIGGINBOTHAM: Yes, Dr. Weiss?

DR. WEISS: Everyone at the Sponsor's panel is extremely knowledgeable and has appeared at many FDA panels, and the standard is that the FDA has all the information. So if there were any inexperienced individuals there, then I could maybe understand some of this. But you've all been here before in various capacities, and so this is a deviation of what is standardly done.

And then it seems to me to be compounded by the fact you

had an extra month. So you prepared for a February 14th meeting, which was called off because of the snowstorm, so you would have had another month to send the material in, and it didn't happen. So it is disturbing to me as a Panel member.

DR. HIGGINBOTHAM: Comment from the Sponsor?

DR. PRICE: I can just comment on the cell count. I only started working on this kind of mid to late January, so some of the analyses I asked for were late. And I think they've had the whole dataset. We just decided to look at it differently than what it was before. And, actually, this is my first Panel meeting.

DR. WEISS: And actually, Frank, yours was the only data that didn't bother me.

(Laughter.)

DR. HIGGINBOTHAM: Any other comments from Sponsor?

DR. SCHALLHORN: This is Dr. Schallhorn again. I just want to comment again on the sensitivity analyses that were done. Again, if you look at the ranges that we were talking about, the scaling here, if we include or exclude those values, it didn't really alter the clinical picture or the clinical results. It didn't alter in a meaningful way the percentage of patients that were 20/20 or better after this surgery. It didn't meaningfully alter the cylinder outcomes, the spherical equivalent outcomes even if you exclude those patients. And I think that's kind of -- it's important to look at in

totality, then, in that regard.

DR. HIGGINBOTHAM: This is Dr. Higginbotham. I have a question I've been dying to ask all day. There was that one slide that randomized patients, as I recall it, freestyle, but I just wonder if the -- and there were 41 patients, so that was 41 patients who were randomized to the TICL; is that right? And I guess the follow-up question is were there other significant number of violations at that site versus others? Just curious.

DR. SCHALLHORN: This is Dr. Schallhorn. That was at the Navy site, and there was 41 -- it was 41 eyes. Listen, I was the principal investigator --

DR. HIGGINBOTHAM: I'm sorry, I didn't mean to insult --

(Laughter.)

DR. SCHALLHORN: That's all right, that's all right. I was the principal investigator. I was the director of refractive surgery for the U.S. Navy. I ran that study. And so I take full responsibility for not ensuring the Agency knew about the randomization. With that said, there were -- that site had no other increase in protocol deviations. Obviously, there were the lens selection and other things that occurred across all the sites.

And one other thing I should mention is the out-of-window, and I mentioned that before. The out-of-window visits were an unfortunate reality of the global war on terrorism, and that came up at about that same time this was happening, and obviously we talked about that.

Now, the randomization, the intention of that randomization was one that clinically made good sense. We wanted to look at the Toric ICL. And by the way, we followed the protocol of the Toric ICL. But we wanted to look at how it compared to the alternative, and the alternative in the military was PRK, because PRK is done about 80% of the time in the military.

And that was the effort. And in that study, which we published several papers on, we looked at things like contrast sensitivity. We looked at night -- we did night driving simulation in those. And the results of those published studies showed a compelling advantage for the Toric ICL.

DR. HIGGINBOTHAM: Well, thank you. I just was curious, but thank you.

Any other questions for the Sponsor? Yes, Dr. Chamberlain?

DR. CHAMBERLAIN: Win Chamberlain. Just a quick question. There was some changes in the online calculator that weren't, I guess, validated in this study. I was just curious what those changes are and if they affect the size of the lens, which may affect vault or other things that haven't been looked at in this study.

MR. HUGHES: No, the actual calculator itself was not validated, but the methodology using it is the same as the methodology used in the MICL calculator. So the way in which the sizes and the power were calculated is the same as for the approved lens.

DR. HIGGINBOTHAM: Mr. Pfleger?

MR. PFLEGER: Yeah, Michael Pfleger. So one quick question. We originally were talking about four axes, 0, 45, 90, 135?

MR. HUGHES: Yes.

MR. PFLEGER: Is that still what you're intended to ask for approval for, or are you now asking for a lot more axes so you don't need the level of fixation, the up to 22.5?

MR. HUGHES: Our current manufacturing process is such that if a surgeon orders a lens that is not in inventory, we will manufacture a lens on the axis of the patient's astigmatism for which that lens is being ordered. But when we make a lens, we don't make single lenses. We make small batches of lenses, and the lenses that are not used for that patient go into inventory. So there will continue to be a range of fixation angles, because I think there was some discussion earlier that it must be difficult to keep a huge range of lenses in inventory, and it is. So we make our lenses to inventory, and if somebody orders one that isn't, then we'll make it to the axis of that particular patient.

DR. HIGGINBOTHAM: Thank you.

Any other questions for Sponsor? Dr. Weiss?

DR. WEISS: So there are 180 -- I'm probably confused on this. I thought there were 80-something degrees of different axes, but there's actually 180 different degrees of possibilities for the --

MR. HUGHES: There is the potential, yes, for us to

manufacture 180 degrees.

DR. WEISS: And do we have experience with that, because, again, we need to look -- as a Panel, we need to look at the data for what you actually have the numbers for. So in terms of the data that you provided, is most of it for the 80-something axes or most of it for the 180 axes, or what was the manufacturing process that was used for the majority of the lenses that were in this study?

MR. HUGHES: It was about 50/50, 50 on the 4 axes, 50 on the 32 axes.

DR. WEISS: Fifty on the 4 axes, 50 on the 32 axes?

MR. HUGHES: 50% on the -- so around about 800 lenses on the 4 axes and about 100 lenses on the 33 axes.

DR. HIGGINBOTHAM: We have a point of clarification from the FDA.

Dr. Eydelman?

DR. EYDELMAN: Dr. Weiss, perhaps you would like to turn to FDA's slide 45. I believe that summarizes the question that you were just asking, summarizes hopefully the answer.

DR. HIGGINBOTHAM: Thank you.

Sponsor, any other last comments you'd like to make? You'll have a chance to come back and do a summation before the vote.

MR. HUGHES: I think there's one comment we would like to

make. There were some questions or comments being made by the FDA on how the lens is positioned in the eye; does it sit on the ciliary process, does it sit in the sulcus. It really depends how you define the sulcus. There is an anatomical term, which is right at the end of the ciliary process, but when we refer to the lens being placed in the sulcus, it's really referring to the ciliary process up into the sulcus.

Dr. Rivera, would you like to come up?

DR. HIGGINBOTHAM: As he's coming up -- this is Dr. Higginbotham -- I have a question. Are the footplates flexible so that -- because people have different anatomy, so it's a matter of actually -- I guess I'm trying to understand whether or not there is a lot of elasticity in terms of those footplates, or flexibility?

MR. HUGHES: Yeah, the footplates are highly flexible, and they have the ability to be crumpled slightly as well. They're about 1.3 mm long, each footplate, and when they get into the -- onto the ciliary process towards the sulcus, they will flex so that the footplates take the shape and the angle of the ciliary process.

DR. RIVERA: Yeah, Dr. Rob Rivera. As to the question of the positioning of the footplates, that's actually something that has continued to be an item of intense study with UBM, primarily. And as we look at sizing and other issues of this sort, it's important to note that at the time of this study, that technology was not available. The assumption would be that the haptics

and footplates would end up residing in the only anatomical location where they could go. Importantly, we don't see any rotational instability nor dislocation or erosion into the zonules or other types of issues.

And the other thing I'd like to point out here, if you'll give me the leeway, is just to indicate to you all that I am a clinician. I also love research. I like to see new technologies brought to patients to see, in fact, if we can test the validity, the safety, and the efficacy. I must say to you that, as a clinician, this is simply the best vision correction surgery that I have ever seen.

I think if I may put it in these terms, the biggest risk to a patient in the Toric ICL study was not an untoward outcome, was not loss of vision, but the potential to end up a casualty of statistics. I would urge you all as clinicians and those of you who have the clinical background to look at the outcomes, to take that into consideration. I would hate for these patients to end up statistical casualties with outstanding outcomes.

Thank you.

DR. HIGGINBOTHAM: Thank you.

Dr. Macsai, one last question?

DR. MACSAI-KAPLAN: I was hoping the Sponsors could just clarify a few things about what they're requesting for approval. And there's three things I'm still muddy on. One, are you proposing that the white-to-white be used, UBM be used, anterior segment OCT be used? What method

are you proposing be used -- this is question number one -- for sizing?

Question No. 2: Are you asking down to -3 spherical equivalent even though your lowest patient was -4.3?

And Question No. 3 is, is your new -- what did you call that one -- algorithm calculator, does that take into account SIA, or surgically induced astigmatism?

DR. VUKICH: This is Dr. Vukich, and I'll start with the sizing. Right now, the DFU for the Myopic ICL is that white-to-white or UBM or other technologies can be used, and so that would be the request that we have. Again, I want to emphasize that other technologies like UBM, one, weren't available at the time, but number two, they have not been validated yet. And so we certainly welcome new technology making this better. We only think it can get better, but the white-to-white data stands on its own, and this is what we have to present, and this is what we are asking for in the DFU with the ability to use other imaging technologies.

The other is -3, and the answer is yes, we are requesting the range as presented in the MICL. It starts at -3 in the MICL, but we would be asking for that with the Toric ICL as well, the same range.

And then finally, the new calculator, would it involve a surgically induced astigmatism. It did not include surgically induced astigmatism, and in spite of that, you saw excellent clinical results. It can only get better if we start factoring in those nuanced -- things that could only

make it better, and the answer is absolutely yes, we would be happy to bring that up and, in fact, as a postmarket study, would look to include that. We think that is appropriate to do, and we're actually excited to do that, because we think we can make what you've seen, which is really good, we think we can make it better by doing that, and we would want to do that.

DR. HIGGINBOTHAM: Dr. Weiss, you have a question?

DR. WEISS: Just a quick question. So half of the patients had the four axes, and half of the patients had the 80 axes, but what's being proposed for approval is 180, but we don't have any patients who've had that? Is my understanding correct?

DR. SCHALLHORN: This is Dr. Schallhorn. Well, I think what was studied was a combination of a 4 and 32 axes, but keep in mind that, from a manufacturing process, all they do is dial in an axis to make the lens. From a surgical planning, it's completely transparent to the surgeon, because the surgeon is just selecting, you know, lens A, B, or C based on the spherical equivalent, what they want spherical equivalent and the postop cylinder. And then lastly, from a surgical perspective, it's simply a matter of looking at the fixation and aligning the lens according to fixation diagram.

DR. VUKICH: So these lenses were identical. They were exactly the same lens, but with the exception that the axis was manufactured at different rotational axes. And so that is the issue. And, of course, quite frankly, the modern standard for global use of this lens is that they are made

on multiple axes and the one that would fit closest to what's there.

Because the protocol was written with the four axes, we can live with that. I mean, if that's what you feel is appropriate, we will do that. Quite frankly, half of the data actually showed other axes, but it's the same lens. It's the exact same lens. It's just where the axis was put in.

DR. HIGGINBOTHAM: So thank you, Sponsor, for a wonderful conversation with the Panel.

Dr. Eydelman, you had a comment?

DR. EYDELMAN: I just wanted to clarify, in light of this comment, I just want to remind everybody that we're here to discuss safety and effectiveness of devices and not procedures. So device as it's currently manufactured is the finished product that we usually study under the PMA and which safety and effectiveness we're here to ascertain.

DR. HIGGINBOTHAM: Okay. Great. So do you want to say something in response to -- Sponsor -- since you haven't left yet? So you get the last word.

DR. VUKICH: We agree. It is the device that needs to be evaluated, and we believe we've shown our case, that with a reasonable assurance of safety and effectiveness, and we welcome the conversation that will follow. Thank you.

DR. HIGGINBOTHAM: Great. Well, thank you. Thank you very much.

Panel, in your folders there are questions. We have one hour to finish the questions, then vote.

(Laughter.)

DR. HIGGINBOTHAM: So we will be very expeditious in this process, but certainly, we want to make sure that all your questions are answered along the way, so please feel free to actually ask questions, make comments along the way.

At this time, let us focus our discussion on the FDA Questions. Panel members, copies are in your folders. I would ask each Panel member identify him or herself each time he or she speaks to facilitate transcription.

Dr. Tieuvi Nguyen, please read the first question.

DR. NGUYEN: Question No. 1: In light of the study conduct, including but not limited to:

- 3,646 data points affected by protocol deviations
- Significant amount of missing data
- Within-window accountability of 70.5% at 12 months
- 68% of eyes implanted with lenses not according to protocol

Do the data generated from the TICL study represent valid scientific evidence for assessment of device safety and effectiveness?

DR. HIGGINBOTHAM: Who would like to lead off on this? I'm going to nominate Dr. Weiss.

DR. WEISS: So I have a lot of residents do resident's day projects with me, and this wouldn't have made it as a resident's day project. So I do understand that this is global, and there's a lot of great data. And as a Panel member maybe -- and the reason I deferred to Dr. Eydelman that question is we may need to look at that data instead of this study. But this was a severely flawed study. And it is what it is.

DR. HIGGINBOTHAM: Would anyone like to counter that comment?

Dr. Glasser and then Dr. Huang?

DR. GLASSER: David Glasser. Yeah, the study was flawed, and it got started off on the wrong foot, and a lot of things didn't go right. But we have what we have, and you know, if you accept that the late and early visits don't matter in terms of being able to assess whether the lens is safe and effective, and you add those late and early visits back, you get up to something like 92% within window. So from that perspective, you know, I'm willing to accept the data as presented and not just disqualify it based on the early and late visits.

DR. HIGGINBOTHAM: Dr. Huang?

DR. HUANG: I basically have the same opinion.

DR. HIGGINBOTHAM: Dr. Chappell?

DR. CHAPPELL: I think I agree with the proposal that we should judge TICL safety by MICL safety, which is better studied. But my problem is,

and I insist, we only have evidence of MICL safety up to eight years. So if I could modify that, for assessment of device safety up to eight years and effectiveness, I would say yes, but then I would have to ask my colleagues whether that safety up to eight years indicates permanent safety for the rest of the patients' lifetimes to our satisfaction. And I'm not an expert in the area to be able to determine that.

DR. HIGGINBOTHAM: So what is your comment regarding the study conduct and the contribution to whether or not we have valid scientific --

DR. CHAPPELL: Regarding that, it was sufficient to determine safety and efficacy up to eight years, up to the amount of follow-up stated. Every study has a limited follow-up, so I can't say that was lack of quality. But I realize that they did have -- that there were missing data, other difficulties mentioned there, but I think they have -- even though it is sloppy, they have managed to convince me of efficacy and safety within the time period discussed. But I'm still worried about that continuing decrease in -- or increase in cell loss.

DR. HIGGINBOTHAM: Any other comments on this question? Yes, Dr. Chamberlain?

DR. CHAMBERLAIN: Yeah, I would just say that in terms of the safety up to eight years, I agree with. The efficacy, though, you could argue that that toric component of it, there may be some unknown variable, some

very small change over time that we couldn't pick up in the first 12 months. And so I think that question is not answered, the efficacy question is not answered.

DR. CHAPPELL: Sorry. I agree. I overspoke on efficacy.

DR. WEISS: And I would -- Jayne Weiss. I would just go to remind the Panel members of this particular question. We'll be getting into safety; we'll be getting into efficacy. We're not talking about the MICL study, and we're not talking about whether we want to approve it. The only question that's being asked in Question No. 1 is did the TICL study represent valid scientific evidence. That's the only question.

DR. HIGGINBOTHAM: Thank you for that clarification. And on that point, I'm going to go back to Dr. Chappell, because you actually started your comment on the MICL. Just looking at the TICL, what is your comment, because you said you were worried about the loss of -- endothelial cell loss, so I'm just trying to get your clarification.

DR. CHAPPELL: I see your point, and sorry for jumping ahead. It seems to me that the lack of quality is not fatal for our purposes.

DR. HIGGINBOTHAM: Okay. Anybody else who would like to -- we have two different sides of this opinion. Dr. Jeng, I see you contemplating.

DR. JENG: I was trying to decide, because Dr. Weiss' comment, her first comment was absolutely valid. This would not have passed with any

of my residents during resident's day project. I think the protocol deviations, the missing data, is kind of sloppy. I know it's out of our hands, out of anybody's hands at this point; we have to deal with what we have. But then on the other hand, I do agree with the others that, you know, I think that using what we have, I think it's reasonable, passable.

DR. HIGGINBOTHAM: Dr. Macsai?

DR. MACSAI-KAPLAN: I have to agree with Dr. Weiss and Dr. Jeng, that if one of my residents brought me this project, I would have issues. I don't, however, have issues with our armed forces personnel being deployed, protecting our country, and being late as a result. So I think you're talking about two different things here. The dataset for 12-month follow-up, a whole bunch of the armed forces people were late. It's unavoidable. That's totally acceptable. It's the other stuff that makes this dataset so cloudy and very difficult to interpret, as a Panel member. And if we're looking at it without the MICL data, for safety, it's not interpretable. It doesn't support one way or the other.

So I would agree with Jayne on Question No. 1. There's too many deviations and lack of validations and not filled in forms regarding rotation, et cetera.

DR. HIGGINBOTHAM: Any other comments?

(No response.)

DR. HIGGINBOTHAM: Dr. Eydelman, with regard to Question

No. 1, the Panel is mixed. However, there was a consensus that there were certainly a lot of drawbacks in the data, missing data, et cetera. However, there was really no consensus whether or not this was impactful as it relates to trying to assess if there is enough scientific evidence to assure safety and efficacy. So we're mixed.

Is there another -- can anyone help clarify that statement beyond that, because we have to come up with a summary.

Yes, Mr. Pfleger?

MR. PFLEGER: Yeah, just a question for you. Do we need to have the definition of valid scientific evidence, because to me, the question you're asking here is, does the data that exists represent valid scientific evidence? That's the first half of the question. For the assessment of safety and efficacy. So we can say, yes, it meets the definition of valid scientific evidence without having to address the question of whether there's enough there to support either safety or efficacy. But I think there's a regulatory definition that needs to be discussed.

MS. FACEY: Yes. Give me one minute as I pull that up, please. This is Natasha Facey.

So valid scientific evidence, as defined in 21 C.F.R. Section 860.7(c)(2), is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts and reports of

significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

DR. HIGGINBOTHAM: Okay. With that -- thank you for that clarification. You know, certainly, I've heard comments about the validity, questioning the validity of the evidence. And if one doesn't have valid scientific evidence, can we be assured of safety and efficacy, or effectiveness, I should say.

Yes?

DR. SAHEB: First of all, I'd like to say all of your residents are really good, because I'm director of resident research at McGill, and a lot of these projects would have been accepted.

(Laughter.)

DR. SAHEB: That being said, I think it's somewhat subjective to decide as a clinician if this -- if the results of this study are valid. And I'd like to defer back to Dr. Chappell, because you started by making a statement, and then I think you might have taken it back. So can you clarify again what your feelings are about this question?

DR. CHAPPELL: I started by making a overbroad statement by

answering further questions regarding MICL, not TICL. So there's far more data from MICL. So, unfortunately, for questions put towards the FDA, I'm not able to answer in black and white. So if I really were to give a truthful answer to that question, it would be barely. Does that make things worse?

(Laughter.)

DR. SAHEB: So is a gentleman's C acceptable?

DR. CHAPPELL: Pardon me?

DR. SAHEB: Is a gentleman's C acceptable?

DR. CHAPPELL: Not in graduate school.

DR. HIGGINBOTHAM: Yeah, okay. Anybody like to -- so Dr. Weiss, I hear you're saying it's not valid and it's --

DR. WEISS: So here's the thing. I'm a clinician.

DR. HIGGINBOTHAM: Yes.

DR. WEISS: And I think, you know, as clinicians, we sort of want one thing, perhaps. And then as looking at the letter of the law, this isn't valid scientific evidence. But this is why I specifically posed the question to FDA, if we don't have a great study, which we don't have, but we do have evidence in other places, can we sort of hedge it and go in another direction. But it doesn't -- the facts don't change. I mean, there's missing -- this is almost like a classic example of how you don't want to do something. There's missing data, so it makes it uninterpretable. We have a whole bunch of explanations. We have a device that has never been used in this study that

they want approval for. I mean, like, huh? How can you -- and this is the Panel to approve a device. So we're being asked to approve a device with 180 degrees that hasn't even been studied. I would say that's the definition of no valid scientific data.

Now, will my answers change on some of these other ones, yeah, they probably will because I have some interest in this, but it doesn't change it. You know, did this particular study -- we're not talking about other studies, we're not talking about articles, we're not talking about individuals here who use the MICL, we're not talking about the MICL study. We're talking about this particular study. There are a tremendous number of flaws in this study, but I don't know if that will kill the rest of the questions. I'm assuming that it won't. And so that's why I'm voicing that point.

And then, just furthermore, I am incredibly disturbed by the fact that there were these other subsets that would have been the opportunity to give the information to FDA and it wasn't given to FDA. So that disturbs me more, because if there was complete transparency, okay, it is what it is, you know, you've inherited some bad things and you make do. But by excluding that information, it doesn't improve it.

DR. HIGGINBOTHAM: So this is Dr. Higginbotham. I'm going to make another stab at this summary. So, Dr. Eydelman, with regard to Question 1, the Panel generally believes that there is not sufficient valid scientific evidence to assure safety and effectiveness.

DR. EYDELMAN: Thank you.

Question No. 2, please?

DR. NGUYEN: Question 2: The applicant has proposed sizing instructions for the Visian Toric Implantable Collamer Lens based on white-to-white and anterior chamber depth measurements which are known to have limitations. Excessive vault and poor vault have been reported in published literature despite various sizing methods used. Furthermore, lens position and vault can impact numerous adverse events such as the formation of cataracts, pigment dispersion, glaucoma, and need for secondary surgical interventions.

a. Based on all available data and the sizing method used in the clinical studies, do you believe that the directions for use concerning sizing are adequate to reasonably ensure predictable and safe postoperative vaulting?

DR. HIGGINBOTHAM: Dr. Macsai?

DR. MACSAI-KAPLAN: On this one, I would say yes. It may sound like I'm contradicting myself, but this is the same sizing method that was used for the MICL. The large body of literature was reviewed both by the Sponsor and the FDA, and that literature's been there for a decade about the MICL. But it hasn't been -- the labeling hasn't changed, it hasn't been withdrawn from market, so yeah.

DR. HIGGINBOTHAM: Does anyone disagree with that

comment?

(No response.)

DR. HIGGINBOTHAM: All right. Let's move on to the part b, and we'll summarize the entire question.

DR. NGUYEN: Does the labeling provide adequate instruction regarding evaluation of postoperative lens vault?

DR. HIGGINBOTHAM: Dr. Zabransky?

DR. ZABRANSKY: Have we actually seen what the labeling says, the black box or the red box or what --

DR. EYDELMAN: It was read in Dr. Macsai's presentation. We can repeat it in a moment if you would prefer.

DR. ZABRANSKY: Um-hum.

DR. HIGGINBOTHAM: Okay.

(Laughter.)

DR. EYDELMAN: It's been a long day. I meant Maryam's presentation. Sorry I misspoke. I obviously need more caffeine. Would you like us to repeat it?

DR. CHAMBERLAIN: Actually, I'd like you to repeat it.

DR. HIGGINBOTHAM: It was an estimate based on central corneal thickness.

DR. ZABRANSKY: Excuse me. I was actually thinking that part of the labeling is instructions for use, and I was thinking of all of that kind of

stuff which we did not see.

DR. HIGGINBOTHAM: Yeah.

DR. MOKHTARZADEH: This is Dr. Mokhtarzadeh. With regard to postoperative Visian TICL vault, it states: "Lens vault, the distance between the anterior surface of the crystalline lens and the posterior surface of the Visian Toric ICL, should be assessed 24 hours postoperatively at a slit lamp." Although the postoperative vault of the Toric ICL is intended to be approximately equal to the central corneal thickness, we believe that the optimal vault should be between 50% and 150% of central corneal thickness. This is being equivalent to a range of 250 to 900 microns. However, in the absence of symptoms, lens vault outside of this range may not necessarily require exchange or removal.

Then under Visian TICL removal, what I read previously in my presentation was: It is recommended that the Visian TICL be removed in cases where the vault is insufficient and the patient exhibits early anterior subcapsular cataract. Removal of the Visian TICL may be necessary in cases where the vault is excessive, causing narrowing of the anterior chamber angle, thus decreasing aqueous flow. Visian TICL removal may also be necessary for other reasons on an individual basis. The risks involved in Visian TICL replacement have not been studied and are unknown.

DR. HIGGINBOTHAM: Dr. Macsai?

DR. MACSAI-KAPLAN: To the best of my recollection, which is

fuzzy, that's very similar to the labeling on the MICL, if not the exact same. It's ½ corneal thickness to 1½ corneal thicknesses. So that's how the MICL is labeled. Sounds good to me.

DR. HIGGINBOTHAM: Any other comments? Dr. Weiss?

DR. WEISS: I would agree with Dr. Macsai.

DR. HIGGINBOTHAM: Dr. Eydelman, in response to Question 2, the Panel generally believes that the available data and sizing method used in these studies, in this study, certainly provides adequate guidance regarding to sizing and that there's also -- the labeling provides adequate instruction regarding evaluation of postoperative lens vault.

DR. EYDELMAN: Thank you.

Question 3?

DR. NGUYEN: Question 3: Potential adverse events identified in the available clinical data pertaining to the TICL lens platform include:

- Inappropriate vault
- Cataract formation
- Secondary surgical interventions
- Endothelial cell loss
- Glaucoma and narrowing of the angle.

Given the available treatment alternatives for lower myopes, do you believe the safety profile of the TICL supports approval of the full range of spherical equivalent powers proposed for approval (-3 to -16D)?

DR. HIGGINBOTHAM: Dr. Weiss?

DR. WEISS: Can I have FDA clarify? For the MICL, what is the range?

DR. EYDELMAN: We will get back to you in a second. I believe it's the same, but we will get back to you in a second.

DR. WEISS: So, again, in terms of what's been studied, if nothing was studied less than 4½, I don't know how you can say that that's safe, except to assume, and I always hate that word, that it's the same as the MICL.

DR. HIGGINBOTHAM: Dr. Eydelman?

DR. EYDELMAN: So we're talking about spherical equivalent, but what we're asking you is to look at the profile of the TICL with its safety and effectiveness and look at the risk/benefit for the patient population proposed for TICL specifically. So it's a bit of a difference.

DR. KIANG: This is Tina Kiang. If I could make a clarifying statement?

DR. HIGGINBOTHAM: Yes.

DR. KIANG: This question takes into account both the sphere and the cylinder range, and as Dr. Hilmantel pointed out before, there's not necessarily a one-to-one relationship between the powers and the power in the corneal plane.

DR. HIGGINBOTHAM: Dr. Eydelman?

DR. EYDELMAN: And I have clarification of MICL. I just didn't want to misspeak. I'll read. Visian MICL is indicated for adults 21 to 45 years of age to correct myopia ranging from -3 diopters to less than or equal to -15 diopters with less than or equal to 2½ diopters of astigmatism at the spectacle plane, and to reduce myopia ranging from greater than 15 diopters to -20 diopters with less than or equal to 2½ diopters of astigmatism at the spectacle plane, and with an anterior chamber depth 3 mm or greater and a stable refractive history, within .5 diopters for one year prior to implantation.

DR. HIGGINBOTHAM: Anyone would like to provide a comment for this question?

Yes, Dr. Saheb?

DR. SAHEB: A comment about some parallels with toric intraocular lenses, and there's so much more we know about toric IOLs today than we did when we first started implanting them. Just last week, I was at a workshop for surgeons who are doing this, and you know, we just started learning about posterior astigmatism. And also, relevant to the point we just made about the power of the intraocular lens and the proportional amount of CYL that might change, that's something that we've learned with time. And I think it's very important to identify that there is that extra amount of knowledge and whether or not this device gets approved, guide the Sponsors moving forward. But I think the reality of any technology is there will be aspects of that technology that will continue to be discovered with time, and

we need to put that in context of whether or not it's unsafe to the patient.

And so I wanted to clarify that point that there's definitely some parallels of the toric IOLs, and I see that it's something that could guide whether or not we -- guide how we move forward but not whether or not we do, just that specific point about the CYL.

DR. HIGGINBOTHAM: We still have a question on the table whether or not, given the alternative treatment alternatives that we have for myopes, if this Panel believes that the safety profile -- and this is a study that didn't actually look at safety; it's relying on the MICL -- so it's almost as if we don't really have the data -- it wasn't actually programmed to actually study for safety. But, nevertheless, we are being asked this question, to believe the safety profile of the TICL supports approval of the full range of spherical equivalent powers proposed for approval.

Dr. Glasser?

DR. GLASSER: David Glasser. So I believe that based on the MICL data that we've reviewed and the TICL data, as limited as it is, in comparison, is sufficient to say that the data supports approval for these listed range of diopter corrections. You know, I think there's always a practice of medicine choice in deciding what's best, you know, glasses, contacts, corneal refractive surgery or intraocular surgery. I think this falls within the limit of reasonableness to approve for this range.

DR. HIGGINBOTHAM: Yes, Saheb, Dr. Saheb?

DR. SAHEB: This is a question to the FDA. Is there a rule for changing what we feel is the appropriate range? So there's always a balance of risk versus benefit, and that balance might be different for somebody who's -3½ versus somebody who's -12½. And so if there are people on the Panel whose comfort level with this risk profile would change as the level of refractive error increases, is there a rule for, even though we're receiving a request for approval of a certain range, changing that range?

DR. EYDELMAN: This is Dr. Eydelman. That is exactly the question. What we're asking is what do you believe the range should be. So you just asked me what's -- that is precisely the question that we're asking you.

DR. HIGGINBOTHAM: So are you feeling we should change the range? Is this something you'd like to propose, and if so, what would be that range?

DR. SAHEB: I think that range should be discussed, and I think that my comfort with a lot of what we discussed today would be different if that range was with higher myopia.

DR. HIGGINBOTHAM: And what is that range that you would propose?

DR. SAHEB: I cannot answer that question.

DR. HIGGINBOTHAM: Does anyone like to propose a different range than what's stated? Dr. Huang?

DR. HUANG: -6.

DR. HIGGINBOTHAM: -6 to -16?

DR. HUANG: Yes.

DR. HIGGINBOTHAM: Going once --

DR. MACSAI-KAPLAN: No, I need clarification. Do you mean -6 sphere, -6 spherical equivalent?

DR. HUANG: Spherical equivalent, -6 --

DR. HIGGINBOTHAM: We're talking about spherical equivalent.

DR. MACSAI-KAPLAN: So that's really -7 plus 2 --

DR. HUANG: If you have astigmatism, yes, yeah.

DR. MACSAI-KAPLAN: This is the Toric ICL --

DR. HIGGINBOTHAM: Dr. Jeng?

DR. JENG: So I think it's actually very difficult to come up with a cutoff. I think we're all thinking the same thing because we're comparing low myopic keratorefractive surgery to intraocular surgery in terms of the risk profile. The problem is, if we just say a -6 or a -7, that doesn't take into account the -4½ who have very thin corneas and they're not candidates for keratorefractive surgery. So I think that drawing a line, you're going to have -- be equivalent to a donut hole that you're going to have people that fall into it, and they can't have either.

DR. HIGGINBOTHAM: Okay.

DR. JENG: And so I think it's very hard to -- even the -3, it's just

very hard to come up with a number. What about a -6, even though I agree it's a subjective cutoff, -6 or not a candidate for keratorefractive surgery. Are we allowed to leave it empty like -- this is Bennie Jeng --

DR. HIGGINBOTHAM: Yes.

DR. JENG: You can leave it empty like that?

DR. HIGGINBOTHAM: These are just recommendations for the FDA to consider. So, Dr. Eydelman, in response to Question 3, the Panel generally believes that the safety profile of the TICL supports approval of a limited range of spherical equivalence, particularly considering that there may be those in the lower stages or lower levels of myopia that may have more alternatives. An offer of -6 to 16 has been put on the table -- that doesn't sound right, does it, as a recommendation -- and other contraindications, such as thin cornea, that would be a contraindication for LASIK and other things as other alternatives.

Dr. Glasser?

DR. GLASSER: I don't know. Maybe it's too late to comment on this, because we've given our recommendation, but --

DR. HIGGINBOTHAM: No, no.

DR. GLASSER: But I really believe that this is something that should be left in the hands of the surgeon to decide because there are just too many variables, as Benny mentioned. There are some -3s who, for whatever reason, you know, don't do well with glasses or contacts and aren't

candidates for keratorefractive surgery. This might be the right thing for them, and I don't think that the risk is necessarily any higher than the MICL.

DR. HIGGINBOTHAM: Thank you. And let me just state, I mean, when I state a summary, it doesn't mean that that's the summary. It's just to really also stimulate some discussion, though, so you followed up very nicely.

Dr. Macsai?

DR. MACSAI-KAPLAN: Dr. Macsai. I guess I have some historical perspective that I want to share with the Panel, having been here when the MICL was approved. This same discomfort with this low range of myopia existed at that time, and I remember we had detailed discussions about should it be 4.5, should it be 5, should it be 5.5. I actually think we might have recommended -5 to -- no, did we recommend -3? But we went over, round and round and round about it. So I think it's very understandable that people find some level of discomfort with this.

But remember that this spherical device is approved to -3. We are now talking about a astigmatic and myopic device. So we're talking a spherical equivalent of -3, so that, actually, it's probably, you know, -4.

DR. HIGGINBOTHAM: Yes, Dr. Weiss?

DR. WEISS: Going down memory lane with Dr. Macsai on the MICL, my recollection was that was -- those were good data, that that meeting was not about what this meeting has been about. So because the

data in this, the TICL, is so problematic, I would agree with my colleagues, restricting or, in some format, the amount of myopia. For example, for the gentleman who spoke about his son, and we don't know what his son was, but let's say his son was a -15, in that case, one could imagine the risk/benefit ratio might be worth it. And I think that's what we're getting to.

I personally don't think we have the data I'd like, but if you have a high myope, and they can't do anything else, and they're miserable, and we've heard some people say, you know, it's worth the risk, then that would be fine. But I would be more hard-pressed to say with what we're seeing here, a -3, would be worth -- -3 plus 1 would be worth the risk.

DR. HIGGINBOTHAM: Okay. Ms. Schwartzott, do you want to comment?

MS. SCHWARTZOTT: I am actually agreeing with limiting the range. I know that there are some exceptions like maybe people in the military, first responders, but for somebody with a mild myopia, I wouldn't take the risk, but for somebody like me or worse, then to me, that would be, you know, a worthwhile risk that the benefit would outweigh.

DR. HIGGINBOTHAM: Thank you.

Ms. Latimer, would you like to comment?

MS. LATIMER: I think, as a consumer, to go over all this information and to understand from the surgeon point of view and to have this surgeon be able to have the discretion, I think that would -- when you

trust your surgeon and the surgeon has the discretion, I think that would be appropriate, working on a patient or a consumer.

DR. HIGGINBOTHAM: So leaving it with the broader range, as opposed to limiting it from the outset? Is that your recommendation?

MS. LATIMER: I would think -- I worry about the donut hole that everyone has been discussing, you know, some patients fall into this place, the donut hole. So the broader ability and leaving it to the surgeon, I think, would be a comfort level as a consumer.

DR. HIGGINBOTHAM: Dr. Macsai?

DR. MACSAI-KAPLAN: I would leave it at -3 to -16 because if the -3 MICL is safe and effective, I don't perceive any difference in a toric versus a spherical for this.

DR. HIGGINBOTHAM: Dr. Eydelman, in response to Question 3, again, I think the Panel is polarized on this. It's very mixed. Some Panelists really think that we should limit the range, with a -6 a potential basement or threshold for this, lower threshold, and others feel that we should keep it from -3 to -16. So it's quite mixed. So unless we have an additional half an hour added onto this meeting, I'm not sure if we have enough brain cells left to actually flesh this out more. But that's the recommendation at this point.

Is that fair, Panel?

UNIDENTIFIED SPEAKER: It's fair.

DR. HIGGINBOTHAM: Okay. Moving on.

DR. NGUYEN: Question 4: Rotational misalignment and axial stability were assessed by direct observation and manifest refraction. In light of the following:

- Limitations of each method
- Missing data (22% of all postop direct measurements)
- Out-of-window visits (123)

Do the rotational misalignment and manifest refraction data provide reasonable assurance that the TICL can achieve desired axial orientation and rotational stability?

DR. HIGGINBOTHAM: Okay. Continuing on this theme, any responses?

Dr. Chamberlain?

DR. CHAMBERLAIN: Well, it seems that -- so in terms of the out-of-window visits, I think maybe we've discussed this a bit, and that may not be as big of a factor, because if we have the data at some point and they have refractive stability, which I think has been fairly well established, that may be the most powerful or compelling argument to say that the refractive -- the patients achieve a refractive stability at the time of the last time point. So I think that's what we need to look at, is the refractive stability.

I think it's impossible from the data we've been presented to know for certain that, especially in patients that have a lower amount of astigmatism in their eye, that those lenses are appropriately aligned. There is

a little bit of uncertainty there. And because the astigmatism is low, we may not have the power to measure an error in rotation or an error in the original alignment.

DR. HIGGINBOTHAM: Dr. Glasser?

DR. GLASSER: I agree with what Dr. Chamberlain said, and I think the purpose of looking for rotational stability and axial orientation is more one of efficacy than safety. And the visual acuity stability data really goes to that. I don't think rotating a lens is going to start tearing zonules and causing trouble, and we haven't seen evidence of that. So I'm in agreement.

DR. HIGGINBOTHAM: Dr. Eydelman?

DR. EYDELMAN: I just wanted to clarify that this is -- nowhere do we state that this is a safety. We're trying to evaluate both safety and effectiveness of this device.

DR. HIGGINBOTHAM: Exactly. And, you know, certainly, we had half of the group had different lenses with different range of degrees, and others had a full scope of what, 33 different possibilities of degrees.

DR. GLASSER: Yeah, David Glasser again. Yes, and I'm not certain that that really makes a whole lot of difference. One of the slides that the Sponsor showed showed that the amount of rotation was about the same whether they used the 4 or the 33, and so the bottom line is probably not going to be much of a difference.

DR. HIGGINBOTHAM: Okay. Anyone disagree with that last

comment?

(No response.)

DR. HIGGINBOTHAM: All right. So, Dr. Eydelman, in response to the Question 4 before us, the Panel generally did not believe that there was any concern with rotational misalignment and felt that, ultimately, the TICL, you know, certainly appears to have the stability that one would expect.

DR. EYDELMAN: And with respect to desired axial orientation?

DR. HIGGINBOTHAM: And desired axial orientation.

DR. EYDELMAN: So I just want to make sure both aspects of the question were addressed --

DR. HIGGINBOTHAM: Okay, let me try to restate that. The Panel generally believes that the rotational alignment and manifest refraction data provide reasonable assurance that the TICL can achieve desired axial orientation and rotational stability. Is that what the Panel is saying?

DR. WEISS: I would say -- this is Jayne Weiss. I don't know.

DR. HIGGINBOTHAM: Okay.

DR. WEISS: So I would put an I don't know --

DR. CHAMBERLAIN: I think the evidence is on -- sorry, Win Chamberlain -- on refractive stability. Rotational stability I would say I don't know as well.

DR. HIGGINBOTHAM: Okay. Well, let's try this again. All right. This is why we state this and make sure that everyone -- I mean, when you

hear it, that this is what you think. So rotational misalignment and manifest refraction data provide reasonable assurance for axial orientation, but we cannot be sure of stability, rotational stability. Is that what I'm hearing? Okay. Does anyone else want to take a stab at this?

Dr. Eydelman, do you have a specific question?

DR. EYDELMAN: I guess I don't have a question. I just want to make sure that in your summary state -- part of your summary was addressing the question on the table, and part was addressing a different issue. So I'm okay with accepting the part that was addressing this, I guess. Not to belabor the point, but the question was about desired axial orientation and rotational stability. Nothing else.

DR. HIGGINBOTHAM: Yeah, correct.

DR. EYDELMAN: Okay.

DR. HIGGINBOTHAM: So on axial orientation, do you have reasonable assurance, Dr. Chamberlain?

DR. CHAMBERLAIN: I would say that we have reasonable assurance -- I'm probably repeating myself here -- we have a reasonable assurance on manifest refractive stability but not on rotational stability. Does that answer the question?

DR. HIGGINBOTHAM: Well, but also axial orientation is part of it.

DR. CHAMBERLAIN: I would say I don't know, so the answer is

no.

DR. HIGGINBOTHAM: Okay. All right. Dr. Jeng, do you agree?

DR. JENG: I fully agree with Dr. Chamberlain.

DR. HIGGINBOTHAM: Okay. So we don't know.

DR. EYDELMAN: Thank you.

DR. HIGGINBOTHAM: Thank you. Thank you for helping with the clarification.

Next question?

DR. NGUYEN: Question 5: Fixation angle is the amount of intraoperative surgical rotation used to achieve the desired TICL axial orientation. 17% of eyes in the Visian TICL study had a fixation angle > 15°. Some published literature indicates that large fixation angles may be associated with greater postoperative rotation. Is there sufficient information available to support directions for use with fixations up to 22.5°, as in the proposed labeling?

DR. HIGGINBOTHAM: Do we have enough information?

Dr. Macsai?

DR. MACSAI-KAPLAN: I'm a little confused by this question after the Sponsors were saying they might have devices available in 180 sizes or 32, 33, whichever, so that you wouldn't have to do a 22.5 fixation angle. So that's why I'm confused, but --

DR. HIGGINBOTHAM: Well, we have a clarification from

Dr. Eydelman.

DR. EYDELMAN: I will try to clarify. My understanding as of today is that while the Sponsor intends to manufacture a device with up to 180 different variation in the axis, that is not to say that the patient, when ordering the lens, the patient will receive the lens with exactly the same orientation. They still want to be able to rotate it up to 22.5. I believe one of the recent presentations which was from one of the people from the Sponsor was trying to address it in that they produce them in bins, and then my understanding is that when they get the order, they send the closest that they have.

DR. HIGGINBOTHAM: So --

DR. EYDELMAN: So they still want to have an option of rotating up to 22.5 --

DR. HIGGINBOTHAM: Yes.

DR. MACSAI-KAPLAN: Okay, so --

DR. EYDELMAN: -- should they not have something closer in stock.

DR. HIGGINBOTHAM: Yes.

Dr. Macsai?

DR. MACSAI-KAPLAN: So this is Dr. Macsai. So now I think I understand the question, and it comes from the horizontal sulcus being shorter than the vertical sulcus, so it has to do with questions of potential tilt

or rotation when you rotate at 22.5 degrees. Is that what we're being asked?

DR. HIGGINBOTHAM: That's one of the factors. Plus the data had, you know, a range of lenses that actually rotated up to, I think, 20 degrees. I don't recall how many were between 20 and 22½ degrees, but most were in the lower ranges of the degree rotation.

DR. MACSAI-KAPLAN: It was a 10.4-degree variation in the 16- to 22-degree group.

DR. HIGGINBOTHAM: So most were in the 10-degree range?

DR. MACSAI-KAPLAN: Right.

DR. HIGGINBOTHAM: Yes. So they all didn't really go up that high. That's one of the questions, so --

Yes, Dr. Eydelman?

DR. EYDELMAN: I believe you're referencing slide 107 in FDA's presentation, for those of you who want to look at it again.

DR. HIGGINBOTHAM: Yeah, there we go. So there were 33 in the 16 to 22, in terms of fixation angle and degrees. That's of the total of 210 eyes as a denominator. Yes. So based on these data, are you comfortable with the use with fixations up to 22½ degrees?

Dr. Glasser?

DR. GLASSER: David Glasser. Well, I guess I'm as comfortable as I was for the last question, which basically means we don't really know how much they rotate. We don't think they rotate a lot because the ones

with high degrees of CYL didn't lose a lot of acuity, but to answer the specific question, I think the answer is we just don't have the data.

DR. HIGGINBOTHAM: Yeah, I think the continuous theme is we just don't have solid data, so it's a matter of being very equivocal in opinions. So I think that's the theme that we're hearing. And these are all very nice people and want to be cooperative in the process, so did you have a comment or --

DR. KIANG: Hi, this is Tina Kiang. I wanted to make sure that the question is understood that it's not how much you believe the lens rotates, but whether the fixation angle, that is, the angle at which the lens is implanted can be at up to 22½ degrees.

DR. HIGGINBOTHAM: And on that note, that's what slide 107 actually displays. So thanks for that reaffirmation.

Okay. So, Dr. Eydelman, in response to Question 5, the Panel continues to have some concern because of the validity of the data, but is -- cannot actually make a strong statement that there is assurance that the use with fixations up to 22½ degrees will be safe and effective.

Dr. Coleman?

DR. COLEMAN: They did have -- yeah, this is Dr. Coleman -- is that it -- that for fixations up to 22 degrees, because they do have patients from 16 to 22 degrees with the fixation. They just had only one greater than 22.

DR. HIGGINBOTHAM: Well, the question is, it's only about 15%, and some of those data were missing, with protocol deviations, et cetera, so I mean, we don't really know the quality of the data within the 33.

DR. COLEMAN: Well --

DR. CHAMBERLAIN: So I don't know if that's actually an unfair distribution for the -- it's a little bit of a small percentage of the whole, and if you look at the worst-case scenario there, which is a 6 -- well, on an average -- it's not worst case, but an average rotational misalignment of 6.8 degrees would throw them off by about, I guess, 20 to 25% of the intended cylindrical power. So I actually -- I don't know if that's unacceptable. I think that's not bad, so --

DR. GLASSER: You've convinced me.

(Laughter.)

DR. HIGGINBOTHAM: They're somewhat comfortable with up to 22½ degrees, but I suppose the emphasis is on somewhat.

DR. EYDELMAN: Question 6, please?

DR. NGUYEN: Question 6: If the device is approved, the applicant is proposing a multicenter, single-arm, prospective post-approval study in 150 patients (up to 300 treated eyes) to evaluate endothelial cell density loss and cataract formation over 5 years, refractive and visual outcomes in higher astigmatism groups over 1 year, and the stability of corrected cylinder and impact of visual disturbance over 1 year. Please

discuss the following:

a. The TICL study did not assess ECD loss. The MICL PAS demonstrated a mean ECD loss of 11% at 5 years. However, 6% of eyes (10 out of 159) had ECD loss greater than 30%. The significance of this result is difficult to interpret due to the lack of an active control arm. In light of this please discuss whether the TICL PAS should:

   i. Include an active control arm?

   ii. Be powered to detect significant differences in the proportion of eyes with large changes (example, >30% loss from baseline)?

DR. HIGGINBOTHAM: Okay. This should be an easier question for us. So we're planning -- Dr. Glasser?

DR. GLASSER: Well, sure, an active control arm is desirable. That would be great. There certainly is a large body of literature saying what normal cell loss is. It has a range, but an active control arm would be desirable. I'd actually want to see it powered to detect a slightly smaller than 30% loss from baseline because these lenses are going to be in people's eyes for a long time. So I'd like to see a larger *n* that could detect a change out at five years of maybe 20% or 15%.

DR. HIGGINBOTHAM: All right.

Dr. Chappell?

DR. CHAPPELL: I continue to be worried about follow-up, so I would prefer follow-up for even more than five years. I realize it's expensive, but I don't know what else to do because there's no way else to get it. These are, by my standards, young people. And I don't know if it's within our purview to suggest continued follow-up of MICL patients who have been treated 5, 10 years ago.

DR. HIGGINBOTHAM: Well, that actually is c, 6c, so if you could hold that comment till 6c about duration of follow-up. Anybody else -- anybody does not feel we need to have an active control arm?

Mr. Pfleger?

MR. PFLEGER: Question. What would the active control be?

DR. HIGGINBOTHAM: Dr. Glasser?

DR. GLASSER: You know, concurrent follow-up of patients in the same age range, followed by the same -- you know, with the same techniques as opposed to historical controls.

MR. PFLEGER: But no surgical intervention?

DR. GLASSER: But no surgical intervention. I wouldn't do sham surgery on them --

MR. PFLEGER: So just a natural history?

DR. GLASSER: -- no, but --

DR. HIGGINBOTHAM: We're going to have to move the discussion along because the hour is quite short. So I think we've heard some

discussion about the control. I think that goes into further defining of the study, but I think there is some consensus there. Perhaps less than 20% of loss from baseline.

Adequacy of the endpoints in the post-approval study, additional endpoints a consideration that needs to be addressed? Any responses to that?

DR. COLEMAN: This is Dr. Coleman, and I wanted to include pigment dispersion and the angle and then transillumination defects as an endpoint.

DR. HIGGINBOTHAM: Noted. Anything else?

(No response.)

DR. HIGGINBOTHAM: Any patient satisfaction instruments? Yes?

DR. MACSAI-KAPLAN: I think it would be very advisable to use some other kind of valid questionnaire. In addition, a valid way of ensuring that there isn't any rotation. I don't know what that is.

DR. HIGGINBOTHAM: Spatial distortion?

DR. MACSAI-KAPLAN: I'm not sure.

DR. HIGGINBOTHAM: Okay.

DR. MACSAI-KAPLAN: I don't know if you take a picture of the eye -- I don't know how you validate that it's stable.

DR. HIGGINBOTHAM: Okay.

DR. CHAMBERLAIN: The FDA in their packet had a mention of a study that was done in Europe, I think, using a photograph technique to establish stability of rotation between two visits, which seem like a reasonable method.

DR. HIGGINBOTHAM: Okay.

Dr. Jeng?

DR. JENG: Along those lines, I was wondering if it would be okay to ask for imaging to confirm location of, like, the footplates and where the lens actually is in the postmarket surveillance since we don't have that data now.

DR. HIGGINBOTHAM: Using UBM as one technology?

DR. JENG: Yeah, whatever technology is available.

DR. HIGGINBOTHAM: And then the last question is safety performance of the device in terms of follow-up. Dr. Chappell, you said longer. What does longer mean?

DR. CHAPPELL: This is Rick Chappell. I would solicit input from the rest of you, but 10 years?

DR. HIGGINBOTHAM: Okay. All right. Any additional feedback, Dr. Eydelman, you need from the question -- oh, Dr. Weiss?

DR. WEISS: I would invoke least burdensome on behalf of the Sponsor. I don't think it's reasonable to have a 10-year study. And also, in terms of where the footplates are, I think I would really like to know that, but

I don't know if that has to be the burden on the Sponsor.

DR. HIGGINBOTHAM: Okay.

Dr. Eydelman, do you need additional feedback on any of these questions?

DR. EYDELMAN: No, let's proceed to voting questions, please.

DR. HIGGINBOTHAM: Summations? Yes. At this time, the Panel will hear summations, comments, or clarifications from the FDA. You have two minutes.

DR. EYDELMAN: Thank you very much for your thoughtful deliberation.

DR. HIGGINBOTHAM: At this time, the Panel will hear summations, comments, or clarification from the Sponsor. You also have two minutes.

Do I take that as a yes or --

UNIDENTIFIED SPEAKER: Yes, yes.

DR. HIGGINBOTHAM: Okay. All right. I didn't hear anything or -- okay. Someone could actually start the summation.

DR. PRICE: I think I'm the last man standing. Okay.

DR. HIGGINBOTHAM: Okay. Dr. Price?

DR. PRICE: Could we have the slides, please? Since I wasn't prepared to do the summation, it'd be nice to have slides. I'm Dr. Francis Price, and hopefully Steve will be back in here in a moment -- maybe not -- if I

could have the next slide.

Oh, here he is, just in time.

DR. SCHALLHORN: Well, thank you. And I apologize for the slight delay. This is Dr. Schallhorn. To recap what you've heard today, the approved Myopic ICL has been a great benefit for our patients. For almost 20 years, hundreds of thousands of patients with up to 20 diopters of myopia have had their lives enhanced with this device. However, there is still an unmet need among patients with myopic astigmatism. Current approved technology has limitations, and for some patients, there are no viable alternatives. The Toric ICL can meet this need with a single procedure that eliminates the associated risks of secondary surgery.

The effectiveness results speak for themselves. As you will recall, 77% of patients had an uncorrected visual acuity at 12 months that was equal to or better than their best-corrected vision before surgery. Remember, these patients had an average of over 9 diopters of myopia and 2 diopters of astigmatism before surgery. At 12 months, the mean spherical equivalent was an impressive 0.03 diopters, with very little variance. And it effectively treated astigmatism. There was nearly a 77% reduction in cylinder, and everything we've looked at points to the lens being rotationally stable. Finally, and importantly, the patients' satisfaction was very high. These results are compelling, given the type of patients that were treated. There is no other technology today that achieves these outcomes.

When we look at the safety profile, the trial confirmed what we knew about the Myopic ICL. The Toric ICL provides good preservation of best-corrected visual acuity, with a low incidence of complications and adverse events.

As a corneal surgeon, I appreciate the discussion about endothelial cell loss today. But what's important to me is that the initial cell loss stabilizes over time, and over 17 years of use has not resulted in any cases of persistent corneal edema, non-traumatic corneal decompensation, or the need for cornea transplantation. I do, however, agree with the need for further follow-up. STAAR is addressing this, as has been discussed just now with post-approval studies.

As we've heard from the STAAR team, they recognize the company should have maintained better compliance. There is no question about that. However, we're here today because an independent audit confirmed the integrity of the study data. We also looked carefully at out-of-window visits, the missed visits, and other protocol deviations to determine their impact on the results.

We conclude with confidence: First, the dataset presented today represents valid scientific evidence to support the meaningful effectiveness and safety conclusions. And, second, the effectiveness findings are so strong, they held up even against the most conservative sensitivity analysis.

So when we look at the totality of the evidence, it's clear to me that the benefits of the Toric ICL are both clinically meaningful, and they're often life-changing to the patients we treat. These benefits far outweigh any potential risks. I join my colleagues today in our strong belief that the Toric ICL should be made available to patients here in the United States.

Thank you again for your time and consideration.

DR. HIGGINBOTHAM: Thank you, Dr. Schallhorn.

At this time, we will proceed to the Panel Vote. I would like to ask our non-voting members, Ms. Jody Latimer, our Consumer Representative; Mr. Michael Pfleger, our Industry Representative; and Ms. Jennifer Schwartzott, our Patient Representative, if they have additional comments.

I'll start with Mr. Pfleger.

MR. PFLEGER: No, I don't.

DR. HIGGINBOTHAM: Ms. Latimer?

MS. LATIMER: No, I don't. Thank you.

DR. HIGGINBOTHAM: Ms. Schwartzott?

MS. SCHWARTZOTT: No, I don't.

DR. HIGGINBOTHAM: Thank you very much. Thank you for your engagement today in our discussion.

We are now ready to vote, Panel, on the Panel's recommendation to the FDA for the Visian Toric Implantable Collamer Lens.

The Panel is expected to respond to three questions related to safety, effectiveness, and benefit versus risk. Ms. Facey will now read three definitions to assist in the premarket approval application voting process. Ms. Facey will also read the proposed indication for use statement for this device.

Ms. Facey?

MS. FACEY: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows. And I will not read valid scientific evidence if that's okay, because I've stated that earlier.

So safety, as defined in 21 C.F.R. Section 860.7(d)(1) - There is a reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any

probable risks.

Effectiveness, as defined in 21 C.F.R. Section 860.7(e)(1) - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results. Again, I will skip reading the definition for valid scientific evidence unless a Panel member would like for that to be reread.

(No response.)

MS. FACEY: Showing no hands, let's proceed.

The Panel will now vote on the Visian Toric Implantable Collamer Lens sponsored by STAAR Surgical. Their proposed IFU is as follows:

DR. NGUYEN: The Visian TICL is indicated for use in adults 21 to 45 years of age for the correction of myopic astigmatism in adults with spherical equivalent ranging from -3 to less than or equal to -15 diopter with cylinder of 1 to 4 diopter; for the reduction of myopic astigmatism in adults with spherical equivalent ranging from greater than -15 to -20 diopter with cylinder 1 to 4 diopters; with an anterior chamber depth of 3 mm or greater when measured from the corneal endothelium to the anterior surface of the crystalline lens and a stable refractive history (within .5 diopter for one year prior to implantation); the Visian TICL is intended for placement in the

posterior chamber (ciliary sulcus) of the phakic eye.

MS. FACEY: Panel members, please locate the voting buttons on your microphone to place your vote of yes, no, or abstain to the following three questions. Just one moment as we pull up the Voting Question No. 1.

So Voting Question 1 reads as follows: Is there reasonable assurance that the Visian Toric Implantable Collamer Lens is safe for use in patients who meet the criteria specified in the proposed indication?

Please vote now: yes, no, or abstain.

(Panel votes.)

MS. FACEY: Voting Question 2: Is there reasonable assurance that the Visian Toric Implantable Collamer Lens is effective for use in the patients who meet the criteria specified in the proposed indication?

Please vote now: yes, no, or abstain.

(Panel votes.)

MS. FACEY: And the final voting question reads as follows: Do the benefits of the Visian Toric Implantable Collamer Lens for use in patients who meet the criteria specified in the proposed indication outweigh the risks for use in patients who meet the criteria specified in the proposed indication?

And please vote now: yes, no, or abstain.

(Panel votes.)

MS. FACEY: And if you could give us a couple of minutes as we tally and verify the official votes? Thank you.

DR. HIGGINBOTHAM: In the meantime, I will now ask the Panel members to discuss their votes. If you answered no to any question, please state whether changes to labeling, restrictions on use, or other controls will make a difference in your answer.

We'll start with Dr. Chappell.

MS. FACEY: Dr. Higginbotham, I'm sorry, I have to read the vote into record first, and then the Panel members will go around and say that they voted.

DR. HIGGINBOTHAM: Thank you. Got ahead of myself.

MS. FACEY: So I'll be reading the tally from this seat here. And on Question No. 1, the Panel voted 5 yes, 1 no, 3 abstain that the data shows that there is reasonable assurance that the Visian Toric Implantable Collamer Lens is safe for use in patients who meet the criteria specified in the proposed indication. And the Panel vote goes as follows: The five yes were Chamberlain, Saheb, Coleman, Zabransky, Glasser; one vote of no, Dr. Huang; and three Panelists have abstained, and that's Dr. Chappell, Dr. Jeng, Dr. Weiss.

Moving on to Question No. 2, the Panel voted 7 yes, 1 no, 1 abstain that the data shows that there is reasonable assurance that the Visian Toric Implantable Collamer Lens is effective for use in patients who meet the criteria specified in the proposed indication. The following Panel members voted yes: Dr. Chamberlain, Glasser, Saheb, Chappell, Huang,

Coleman, Jeng; Dr. Zabransky voted no; and Dr. Weiss abstained.

On Question No. 3, the Panel voted 6 yes and 3 -- excuse me -- on Question No. 3, the Panel voted 6 yes, 0 noes, 3 abstains that the benefits of the Visian Toric Implantable Collamer Lens do outweigh the risks for use in patients who meet the criteria specified in the proposed indication. The Panelists voted as 6 yes: Dr. Chamberlain, Glasser, Chappell, Huang, Coleman, Zabransky; 3 abstaining being Dr. Jeng, Dr. Saheb, and Dr. Weiss.

And I'm sorry, I just want to state for the record Dr. Marian Macsai-Kaplan did leave prior to the vote, and her vote was not captured for today. And that completes the voting questions. Thank you.

DR. HIGGINBOTHAM: Thank you. Now I will ask Panel members to discuss their votes. And if you answered no to any questions, please state whether changes to labeling, restrictions on use, or other controls would make a difference in your answer.

Dr. Chappell?

DR. CHAPPELL: Do you ask for comments from abstainers?

DR. HIGGINBOTHAM: Yes.

DR. CHAPPELL: My main worry with regards to the abstention of Voting Question 1 is endothelial cell loss, corneal endothelial cell loss, and I'd like to see more evidence from either MICL or TICL with regards to long-term cell loss.

DR. HIGGINBOTHAM: Thank you. Dr. Coleman? Well, do you

have any comments?

DR. COLEMAN: No, no comments.

DR. HIGGINBOTHAM: Dr. Glasser?

DR. GLASSER: No comments.

DR. HIGGINBOTHAM: All right. Dr. Saheb?

DR. SAHEB: I abstained for the last question, and the vote would change to a yes if the proposed indications were mildly modified and some guidance for the PAS studies.

DR. HIGGINBOTHAM: Thank you.

Dr. Huang?

DR. HUANG: I voted no for the first question for the following reason: First, I think the endothelial density data safety issue is not totally settled. And second is that I do believe that, you know, the patient with higher myopia and higher amount of astigmatism may directly benefit from this technology. However, the current indications seem to be too broad for me.

DR. HIGGINBOTHAM: Thank you.

Dr. Jeng?

DR. JENG: I voted yes on the second question and abstained from the first and the third one. The reasons are the endothelial cell count. The safety data is based on the MICL data, which we saw, and I do want to see more endothelial cell count data. And the surgery itself, there is a little

bit more manipulation, so I mean, I think that in the postmarket data, that will be very telling. I was convinced about the efficacy. And because of my voting on the first one, I voted the same way on the third question.

DR. HIGGINBOTHAM: Thank you.

Dr. Weiss?

DR. WEISS: I abstained on all three questions. I'd like to see approval for patients in whom the benefits outweigh the risks, such as those patients who are higher myopes or maybe those who cannot have any other refractive procedures. I would, though, ask the FDA and the Sponsor consider developing a standard consent form for the potential candidates for this to ensure no patient is given unrealistic expectations that this is a trivial procedure, and this is because I'm a veteran of the 2008 LASIK meeting in which this came up again and again.

I think the Panel has been put in an impossible situation of voting for device approval that patients and MDs might want on the basis of a highly flawed study that cannot give us the answers to the questions we were asked.

DR. HIGGINBOTHAM: Thank you.

Dr. Chamberlain?

DR. CHAMBERLAIN: I voted yes on all three and, I think, with trepidation on all three because of the nature of the study, and that was my biggest concern is the way it was carried out. Hopefully, the PAS study will

be carried out in a more reasonable fashion along with some of the recommendations that were made today. I do believe that this technology has tremendous promise for certain individuals.

DR. HIGGINBOTHAM: Dr. Zabransky?

DR. ZABRANSKY: I voted no on the second question, but I really vacillated on that one in my mind and probably should have abstained. I think that the issue of the effectiveness can really be addressed with a good PAS. Data really has to -- and maybe even the remassaging of some of the data by the Sponsor that they screwed up on, what they were presenting.

DR. HIGGINBOTHAM: Well, Panel, it's been a long day. I would like to thank all of you for your deliberation on this application, and I must say that this was probably one of the most difficult panels that I've had the privilege of chairing, but your esprit de corps made it a pleasant experience, at least, and I'd like to thank you for your patience.

And, FDA, I'd like to thank you for your presentations and your in-depth analyses and your thoughtful comments.

I'd like to thank the Sponsor as well for bringing this product before us for our consideration.

Dr. Eydelman, would you like to make some comments?

DR. EYDELMAN: I would like to thank all the Panelists for, first of all, coming back a month after you were supposed to come. Many of you have cancelled clinics and modified your schedules at the last minute, and I

want to personally thank you for your service to the public health and for your thoughtful deliberations.

And last, but certainly not least, I want to thank my team, who has spent many weekends, many nights trying to go through volumes and volumes of data.

Thank you.

(Applause.)

DR. CHAPPELL: And the administrative team for scheduling us twice.

(Laughter.)

DR. HIGGINBOTHAM: Thank you, everyone, and safe travels, and stay warm.

(Whereupon, at 6:21 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

OPHTHALMIC DEVICES PANEL MEETING

March 14, 2014

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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